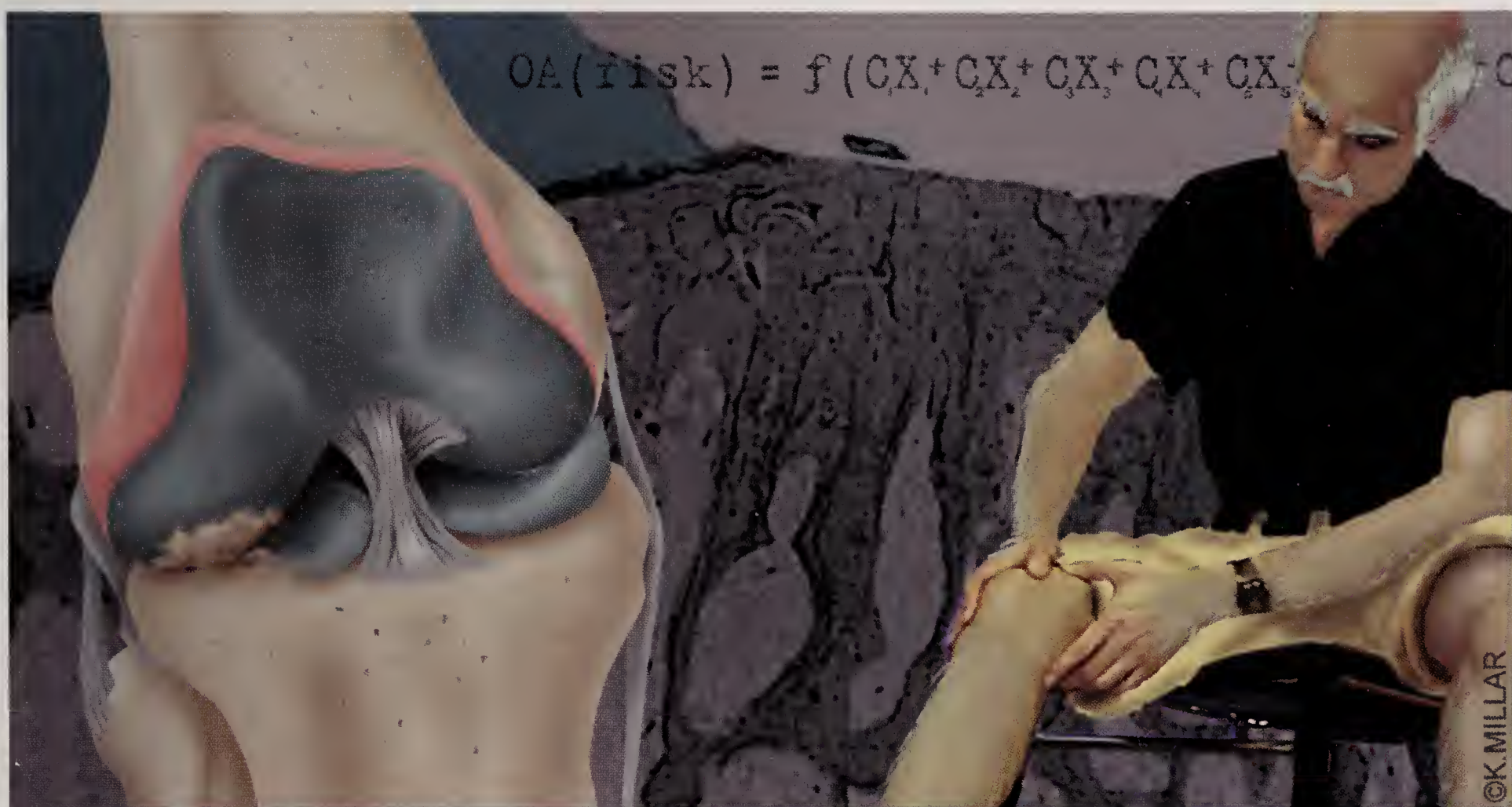




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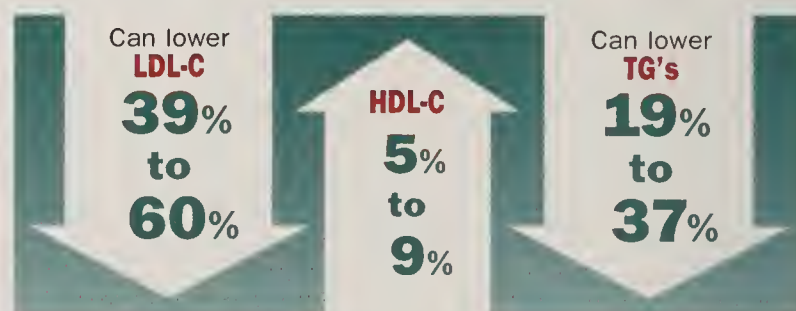
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LIPITOR is a HMG-CoA reductase inhibitor (statin). LIPITOR is indicated as an adjunct to diet for the reduction of elevated total cholesterol, LDL-C, triglycerides, and apolipoprotein B in patients with primary hypercholesterolemia, mixed dyslipidemia (including familial combined hyperlipidemia) or heterozygous familial hypercholesterolemia, when diet and other nonpharmacological measures have been inadequate.

See prescribing information for important patient screening and monitoring information.

LIPITOR is contraindicated during pregnancy and lactation.

Caution should be exercised in severely hypercholesterolemic patients who are also severely renally impaired, elderly, or are concomitantly being administered digoxin or erythromycin.

See prescribing information for complete contraindications, warnings, precautions, dosing and administration. Product monograph available on request.

* In dose response studies in mildly to moderately hyperlipidemic patients (Fredrickson Type IIa and IIb) with LIPITOR 10-80 mg.

† At starting doses. Results in mildly to moderately hyperlipidemic patients (Fredrickson Type IIa and IIb). One year, double-blind, randomized multicentre study.

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It is with great pleasure that we bring to you the second issue of the 76th Volume of the *UTMJ*. We are delighted to offer an excellent balance of clinical and basic science articles that truly reflect the interests of the students within the Faculty of Medicine at the University of Toronto.

From a clinical perspective, two excellent original papers are presented that will undoubtedly be perused by clinicians and students alike. Lieberman and Birdi have written a highly informative review of post-streptococcal arthritis that highlights some of the major challenges in diagnosis and management. Droll and Marks have provided a comprehensive look at the risk factors for osteoarthritis in the anterior cruciate ligament deficient knee.

From a basic research perspective, we are excited to present two fascinating articles from the highly dynamic fields of neuroscience and gene therapy. Hebb has written a formidable review of Huntington's Disease ranging from the neurological and psychological manifestations to the underlying genetic defect. Lax and Lui have reviewed the promising field of cancer gene therapy with a thorough discussion of its rationale and the technical challenges that remain.

Our feature sections pick-up where the December issue left off. In Morning Report, chest pain is further examined from a different perspective than last issue's discussion of myocardial infarction. In News and Views, our series on Complementary and Alternative Medicine continues with a practical summary of the many alternative therapies, their risks and benefits. Quick Diagnosis focuses on internal medicine with a number of challenging cases for both the student and the practitioner. Last, but definitely not least, Book and Technology Reviews keep our readers abreast of new publications and methodologies in the laboratory.

We are indebted once again to the many section editors, contributors and illustrators that have enabled us to provide what we believe to be a thought-provoking and educational issue that lives up to the high standards of the *UTMJ*. We hope that you will agree with our sentiments.

Sincerely,

Sandra Demaries, MSc.
George Thanassoulis, BSc.
Editors-in-Chief

UTMJ

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LIPITOR*
(Atorvastatin Calcium)
10 mg, 20 mg and 40 mg tablets

THERAPEUTIC CLASSIFICATION: Lipid Metabolism Regulator

ACTIONS AND CLINICAL PHARMACOLOGY

LIPITOR (atorvastatin calcium) is a synthetic lipid-lowering agent. It is a selective, competitive inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, which is an early and rate-limiting step in the biosynthesis of cholesterol.

LIPITOR lowers plasma cholesterol and lipoprotein levels by inhibiting HMG-CoA reductase and cholesterol synthesis in the liver and by increasing the number of hepatic Low Density Lipoprotein (LDL) receptors on the cell-surface for enhanced uptake and catabolism of Low Density Lipoprotein (LDL).

LIPITOR reduces LDL-Cholesterol (LDL-C) and the number of LDL particles, and lowers Very Low Density Lipoprotein-Cholesterol (VLDL-C) and serum triglycerides (TG), as well as the number of apolipoprotein B (apo B) containing particles.

Atorvastatin is rapidly absorbed after oral administration; maximum plasma concentrations occur within 1 to 2 hours. Atorvastatin tablets are 95% to 99% bioavailable compared to solutions.

Mean distribution of atorvastatin is approximately 565 liters. Atorvastatin is ≥98% bound to plasma proteins. Atorvastatin is extensively metabolized by cytochrome P-450 3A4 to ortho- and parahydroxylated derivatives and various beta-oxidation products. Approximately 70% of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites.

Atorvastatin and its metabolites are eliminated by biliary excretion. Less than 2% of a dose of atorvastatin is recovered in urine following oral administration. Mean plasma elimination half-life of atorvastatin in humans is approximately 14 hours, but the half-life of inhibitory activity for HMG-CoA reductase is 20 to 30 hours due to the contribution of longer-lived active metabolites.

INDICATIONS AND CLINICAL USE

LIPITOR (atorvastatin calcium) is indicated as an adjunct to diet, at least equivalent to the American Heart Association (AHA) Step 1 diet, for the reduction of elevated total cholesterol, LDL-C, triglycerides (TG) and apolipoprotein B (apo B) in hyperlipidemic and dyslipidemic conditions, when response to diet and other nonpharmacological measures alone has been inadequate, including:

- Primary hypercholesterolemia (Type IIa),
- Combined (mixed) hyperlipidemia (Type IIb), including familial combined hyperlipidemia, regardless of whether cholesterol or triglycerides are the lipid abnormality of concern, and
- Heterozygous familial hypercholesterolemia.

In clinical trials, LIPITOR (10-80 mg/day) significantly improved lipid profiles in patients with a wide variety of hyperlipidemic and dyslipidemic conditions. In 2 dose-response studies in mildly to moderately hyperlipidemic patients (Fredrickson Types IIa and IIb), LIPITOR reduced the levels of total cholesterol (29-45%), LDL-C (39-60%), apo B (32-50%), TG (19-37%), and increased HDL-C levels (5-9%). Comparable responses were achieved in patients with heterozygous familial hypercholesterolemia, non-familial forms of hypercholesterolemia, combined hyperlipidemia, including familial combined hyperlipidemia and patients with non-insulin dependent diabetes mellitus. In patients with hypertriglyceridemia (TG>350 mg/dL), LIPITOR lowered TG levels by 27-42%. Limited data is available in homozygous familial hypercholesterolemia (FH). An open-label study with atorvastatin 80 mg/day in homozygote FH patients showed a LDL-C lowering of 30% for patients not on plasmapheresis and of 31% for patients who continued plasmapheresis. A LDL-C lowering of 35% was observed in receptor defective patients and of 19% in receptor negative patients (see PHARMACOLOGY, Clinical Studies).

For more details on efficacy results by pre-defined classification and pooled data by Fredrickson types, see PHARMACOLOGY, Clinical Studies.

Prior to initiating therapy with LIPITOR, secondary causes should be excluded for elevations in plasma lipid levels (e.g. poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemias, obstructive liver disease, and alcoholism), and a lipid profile performed to measure total cholesterol, LDL-C, HDL-C, and TG. For patients with TG <4.52 mmol/L (<400 mg/dL), LDL-C can be estimated using the following equation:

$$\text{LDL-C (mmol/L)} = \text{total cholesterol} - [(0.37 \times (\text{TG} + \text{HDL-C}))]$$

$$\text{LDL-C (mg/dL)} = \text{total cholesterol} - [(0.2 \times (\text{TG} + \text{HDL-C}))]$$

For patients with TG levels >4.52 mmol/L (>400 mg/dL), this equation is less accurate and LDL-C concentrations should be determined by ultracentrifugation.

CONTRAINDICATIONS

Hypersensitivity to any component of this medication.

Active liver disease or unexplained persistent elevations of serum transaminases exceeding 3 times the upper limit of normal (see WARNINGS).

Pregnancy and lactation (see PRECAUTIONS).

WARNINGS

Pharmacokinetic Interactions

The use of HMG-CoA reductase inhibitors has been associated with severe myopathy, including rhabdomyolysis, which may be more frequent when they are co-administered with drugs that inhibit the cytochrome P-450 enzyme system. Atorvastatin is metabolized by cytochrome P-450 isoform 3A4 and as such may interact with agents that inhibit this enzyme (see WARNINGS, Muscle Effects and PRECAUTIONS, Drug Interactions and Cytochrome P-450-mediated Interactions).

Hepatic Effects

In clinical trials, persistent increases in serum transaminases greater than three times the upper limit of normal occurred in <1% of patients who received LIPITOR. When the dosage of LIPITOR was reduced, or when drug treatment was interrupted or discontinued, serum transaminase levels returned to pretreatment levels. The increases were generally not associated with jaundice or other clinical signs or symptoms. Most patients continued treatment with a reduced dose of LIPITOR without clinical sequelae.

Liver function tests should be performed before the initiation of treatment, and periodically thereafter. Special attention should be paid to patients who develop elevated serum transaminase levels, and in these patients measurements should be repeated promptly and then performed more frequently.

If increases in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) show evidence of progression, particularly if they rise to greater than 3 times the upper limit of normal and are persistent, the dosage should be reduced or the drug discontinued.

LIPITOR should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease. Active liver disease or unexplained transaminase elevations are contraindications to the use of LIPITOR; if such a condition should develop during therapy, the drug should be discontinued.

Muscle Effects

Myopathy, defined as muscle aching or muscle weakness in conjunction with increases in creatinine phosphokinase (CPK) values to greater than ten times the upper limit of normal, should be considered in any patient with diffuse myalgia, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. LIPITOR therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected.

Friedewald, WT et al. *Clin Chem* 1972; 18(6):489-502.



The risk of myopathy and rhabdomyolysis during treatment with HMG-CoA reductase inhibitors is increased with concurrent administration of cyclosporine, fibric acid derivatives, erythromycin, niacin (nicotinic acid), azole antifungals or nefazodone. As there is no experience to date with the use of LIPITOR given concurrently with these drugs, with the exception of a pharmacokinetic study with erythromycin, the benefits and risks of such combined therapy should be carefully considered (see PRECAUTIONS, Drug Interactions).

Rhabdomyolysis has been reported in very rare cases with LIPITOR (see PRECAUTIONS, Drug Interactions). Rhabdomyolysis with renal dysfunction secondary to myoglobinuria has also been reported with HMG-CoA reductase inhibitors. LIPITOR therapy should be temporarily withheld or discontinued in any patient with an acute serious condition suggestive of a myopathy or having a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis (such as severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders, and uncontrolled seizures).

PRECAUTIONS

General

The effects of atorvastatin-induced changes in lipoprotein levels, including reduction of serum cholesterol on cardiovascular morbidity or mortality or total mortality have not been established.

Before instituting therapy with LIPITOR (atorvastatin calcium), an attempt should be made to control elevated serum lipoprotein levels with appropriate diet, exercise, and weight reduction in overweight patients, and to treat other underlying medical problems (see INDICATIONS AND CLINICAL USE). Patients should be advised to inform subsequent physicians of the prior use of LIPITOR or any other lipid-lowering agents.

Effect on the Lens

Current long-term data from clinical trials do not indicate an adverse effect of atorvastatin on the human lens.

Effect on Ubiquinone (CoQ₁₀) Levels

Significant decreases in circulating ubiquinone levels in patients treated with atorvastatin and other statins have been observed. The clinical significance of a potential long-term statin-induced deficiency of ubiquinone has not been established. It has been reported that a decrease in myocardial ubiquinone levels could lead to impaired cardiac function in patients with borderline congestive heart failure (see SELECTED BIBLIOGRAPHY).

Effect on Lipoprotein(a)

In some patients, the beneficial effect of lowered total cholesterol and LDL-C levels may be partly blunted by a concomitant increase in Lp(a) levels. Until further experience is obtained, it is suggested, where feasible, that measurements of serum Lp(a) be followed up in patients placed on atorvastatin therapy (see SELECTED BIBLIOGRAPHY).

Hypersensitivity

An apparent hypersensitivity syndrome has been reported with other HMG-CoA reductase inhibitors which has included 1 or more of the following features: anaphylaxis, angioedema, lupus erythematosus-like syndrome, polymyalgia rheumatica, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, eosinophilia, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome. Although to date hypersensitivity syndrome has not been described as such, LIPITOR should be discontinued if hypersensitivity is suspected.

Use in Pregnancy

LIPITOR is contraindicated during pregnancy (see CONTRAINDICATIONS).

Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they may cause harm to the fetus when administered to pregnant women.

There are no data on the use of LIPITOR during pregnancy. LIPITOR should be administered to women of child-bearing age only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the patient becomes pregnant while taking LIPITOR, the drug should be discontinued and the patient apprised of the potential risk to the fetus.

Nursing Mothers

In rats, milk concentrations of atorvastatin are similar to those in plasma. It is not known whether this drug is excreted in human milk. Because of the potential for adverse reactions in nursing infants, women taking LIPITOR should not breast-feed (see CONTRAINDICATIONS).

Pediatric Use

Treatment experience in a pediatric population is limited to doses of LIPITOR up to 80 mg/day for 1 year in 8 patients with homozygous familial hypercholesterolemia. No clinical or biochemical abnormalities were reported in these patients.

Geriatric Use

Treatment experience in adults 70 years or older (N=221) with doses of LIPITOR up to 80 mg/day has demonstrated that the safety and effectiveness of atorvastatin in this population was similar to that of patients <70 years of age. Pharmacokinetic evaluation of atorvastatin in subjects over the age of 65 years indicates an increased AUC. As a precautionary measure, the lowest dose should be administered initially (see PHARMACOLOGY, Human Pharmacokinetics; and SELECTED BIBLIOGRAPHY).

Renal Insufficiency

Plasma concentrations and LDL-C lowering efficacy of LIPITOR are similar in patients with moderate renal insufficiency compared with patients with normal renal function. However, since several cases of rhabdomyolysis have been reported in patients with a history of renal insufficiency of unknown severity, as a precautionary measure and pending further experience in renal disease, the lowest dose (10 mg/day) of LIPITOR should be used in these patients. Similar precautions apply in patients with severe renal insufficiency (creatinine clearance <30 mL/min); the lowest dosage should be used and implemented cautiously (see WARNINGS, Muscle Effects; PRECAUTIONS, Drug Interactions). Refer also to DOSAGE AND ADMINISTRATION.

Endocrine Function

HMG-CoA reductase inhibitors interfere with cholesterol synthesis and as such might theoretically blunt adrenal and/or gonadal steroid production. Clinical studies with atorvastatin and other HMG-CoA reductase inhibitors have suggested that these agents do not reduce plasma cortisol concentration or impair adrenal reserve and do not reduce basal plasma testosterone concentration. However, the effects of HMG-CoA reductase inhibitors on male fertility have not been studied in adequate numbers of patients. The effects, if any, on the pituitary-gonadal axis in premenopausal women are unknown.

Patients treated with atorvastatin who develop clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution should be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients receiving other drugs (e.g. ketoconazole, spironolactone or cimetidine) that may decrease the levels of endogenous steroid hormones.

Drug Interactions

Concomitant Therapy with Other Lipid Metabolism Regulators: Combined drug therapy should be approached with caution as information from controlled studies is limited.

Bile Acid Sequestrants:

Patients with mild to moderate hypercholesterolemia: LDL-C reduction was greater when LIPITOR 10 mg and colestipol 20 g were coadministered (~45%) than when either drug was administered alone (~35% for LIPITOR and ~22% for colestipol).

Patients with severe hypercholesterolemia: LDL-C reduction was similar (~53%) when LIPITOR 40 mg and colestipol 20 g were coadministered when compared to that of LIPITOR 80 mg alone. Plasma concentration of



atorvastatin was lower (approximately 26%) when LIPITOR 40 mg plus colestipol 20 g were coadministered compared to LIPITOR 40 mg alone.

However, the combination drug therapy was less effective in lowering the triglycerides than LIPITOR monotherapy in both types of hypercholesterolemic patients (see PHARMACOLOGY, Clinical Studies).

When LIPITOR is used concurrently with colestipol or any other resin, an interval of at least 2 hours should be maintained between the two drugs, since the absorption of LIPITOR may be impaired by the resin.

Fibric Acid Derivatives (Gemfibrozil, Fenofibrate, Bezafibrate) and Niacin (Nicotinic Acid): Although there is no experience with the use of LIPITOR given concurrently with fibric acid derivatives and niacin, the benefits and risks of such combined therapy should be carefully considered. The risk of myopathy during treatment with other drugs in this class is increased with concurrent administration (see WARNINGS, Muscle Effects).

Coumarin Anticoagulants: LIPITOR had no clinically significant effect on prothrombin time when administered to patients receiving chronic warfarin therapy (see SELECTED BIBLIOGRAPHY).

Digoxin: Coadministration of multiple doses of LIPITOR and digoxin increased steady-state plasma digoxin concentrations by approximately 20%. Patients taking digoxin should be monitored closely and appropriately.

Oral Contraceptives: Coadministration of LIPITOR with an oral contraceptive, containing 1 mg norethindrone and 35 µg ethinyl estradiol, increased plasma concentrations (AUC levels) of norethindrone and ethinyl estradiol by approximately 30% and 20%, respectively. These increases should be considered when selecting an oral contraceptive.

Antacids: Administration of aluminum and magnesium based antacids, such as Maalox® TC Suspension, with LIPITOR decreased plasma concentrations of LIPITOR by approximately 35%. LDL-C reduction was not altered but the triglyceride-lowering effect of LIPITOR may be affected.

Cimetidine: Administration of cimetidine with LIPITOR did not alter plasma concentrations or LDL-C lowering efficacy of LIPITOR, however, the triglyceride-lowering effect of LIPITOR was reduced from 34% to 26%.

Cytochrome P-450-mediated Interactions: Atorvastatin is metabolized by the cytochrome P-450 isoenzyme, CYP 3A4. Erythromycin, a CYP 3A4 inhibitor, increased atorvastatin plasma levels by 40%. Coadministration of CYP 3A4 inhibitors, such as grapefruit juice, macrolide antibiotics (including erythromycin), immunosuppressants (cyclosporin), azole antifungal agents (i.e. itraconazole, ketoconazole), or some antidepressants (e.g. nefazodone), may have the potential to increase plasma concentrations of HMG CoA reductase inhibitors, including LIPITOR (see SELECTED BIBLIOGRAPHY). Caution should thus be exercised with concomitant use of these agents (see WARNINGS, Pharmacokinetic Interactions, Muscle Effects; DOSAGE AND ADMINISTRATION).

In a study with healthy subjects, coadministration of maximum doses of both atorvastatin (80 mg) and terfenadine (120 mg), a CYP 3A4 substrate, was shown to produce modest increases in AUC values. The QTc interval remained unchanged. However, since an interaction between these two drugs cannot be excluded in patients with predisposing factors for arrhythmia, (e.g. preexisting prolonged QT interval, severe coronary artery disease, hypokalemia), caution should be exercised when these agents are coadministered (see WARNINGS, Pharmacokinetic Interactions; DOSAGE AND ADMINISTRATION).

Antipyrine: Antipyrine was used as a non-specific model for drugs metabolized by the microsomal hepatic enzyme system (cytochrome P-450 system). LIPITOR had no effect on the pharmacokinetics of antipyrine, thus interactions with other drugs metabolized via the same cytochrome isozymes are not expected.

Erythromycin: In healthy individuals, plasma concentrations of atorvastatin increased approximately 40% with coadministration of LIPITOR and erythromycin, a known inhibitor of CYP 3A4 (see WARNINGS, Muscle Effects).

Other Concomitant Therapy: In clinical studies, LIPITOR was used concomitantly with antihypertensive agents and estrogen replacement therapy without evidence to date of clinically significant adverse interactions. Interaction studies with specific agents have not been conducted.

Patients with Severe Hypercholesterolemia: Higher drug dosages (80 mg/day) required for some patients with heterozygous familial hypercholesterolemia or severe hypercholesterolemia are associated with increased plasma levels of atorvastatin. **Caution should be exercised in such patients who are also severely renally impaired, elderly, or are concomitantly being administered digoxin or CYP 3A4 inhibitors (see WARNINGS, Pharmacokinetic Interactions, Muscle Effects; PRECAUTIONS, Drug Interactions and DOSAGE AND ADMINISTRATION).**

Drug/Laboratory Test Interactions

LIPITOR may elevate serum transaminase and creatinine phosphokinase levels (from skeletal muscle). In the differential diagnosis of chest pain in a patient on therapy with LIPITOR, cardiac and noncardiac fractions of these enzymes should be determined.

ADVERSE REACTIONS

LIPITOR is generally well-tolerated. Adverse reactions have usually been mild and transient. In controlled clinical studies (placebo-controlled and active-controlled comparative studies with other lipid lowering agents) involving 2502 patients, <2% of patients were discontinued due to adverse experiences attributable to LIPITOR. Of these 2502 patients, 1721 were treated for at least 6 months and 1253 for 1 year or more.

Adverse experiences occurring at an incidence ≥1% in patients participating in placebo-controlled clinical studies of LIPITOR and reported to be possibly, probably or definitely drug related are shown in Table 1 below:

TABLE 1. Associated Adverse Events Reported in ≥ 1% of Patients in Placebo Controlled Clinical Trials

	Placebo % (n=270)	LIPITOR % (n=1122)
GASTROINTESTINAL		
Constipation	1	1
Diarrhea	1	1
Dyspepsia	2	1
Flatulence	2	1
Nausea	0	1
NERVOUS SYSTEM		
Headache	2	1
MISCELLANEOUS		
Pain	<1	1
Myalgia	1	1
Asthenia	<1	1

The following additional adverse events were reported in clinical trials; not all events listed below have been associated with a causal relationship to LIPITOR therapy: Muscle cramps, myositis, myopathy, paresthesia, peripheral neuropathy, pancreatitis, hepatitis, cholestatic jaundice, anorexia, vomiting, alopecia, pruritus, rash, impotence, hyperglycemia, and hypoglycemia.

Post-marketing experience: Very rare reports of severe myopathy with or without rhabdomyolysis have been reported (see WARNINGS, Muscle Effects; PRECAUTIONS, Renal Insufficiency and Drug Interactions).

Ophthalmologic observations: see PRECAUTIONS.

Laboratory Tests: Increases in serum transaminase levels have been noted in clinical trials (see WARNINGS).

SYMPTOMS AND TREATMENT OF OVERDOSAGE

There is no specific treatment for atorvastatin overdose. Should an overdose occur, the patient should be treated symptomatically and supportive measures instituted as required. Due to extensive drug binding to plasma proteins, hemodialysis is not expected to significantly enhance atorvastatin clearance.

DOSAGE AND ADMINISTRATION

Patients should be placed on a standard cholesterol-lowering diet [at least equivalent to the American Heart Association (AHA) Step 1 diet] before receiving LIPITOR, and should continue on this diet during treatment with

LIPITOR. If appropriate, a program of weight control and physical exercise should be implemented.

Primary Hypercholesterolemia and Combined (Mixed) Hyperlipidemia, Including Familial Combined Hyperlipidemia

The recommended dose of LIPITOR is 10 mg once a day. The majority of patients achieve and maintain target cholesterol levels with LIPITOR 10 mg/day. A significant therapeutic response is evident within 2 weeks, and the maximum response is usually achieved within 2-4 weeks. The response is maintained during chronic therapy. Doses can be given at any time of the day, with or without food, and should preferably be given in the evening.

Doses should be individualized according to baseline LDL-C levels, the desired LDL-C target (such as that recommended by the US National Cholesterol Education Program [NCEP] and/or the Canadian Consensus Conference Guidelines), the goal of therapy and the patient's response. Adjustments of dosage, if necessary, should be made at intervals of 4 weeks or more. The recommended dose range for most patients is 10 to 40 mg/day. The maximum dose is 80 mg/day, which may be required in a minority of patients (see section below).

Cholesterol levels should be monitored periodically and consideration should be given to reducing the dosage of LIPITOR if cholesterol falls below the targeted range such as that recommended by guidelines.

The following reductions in total cholesterol and LDL-C levels have been observed in 2 dose-response studies, and may serve as a guide to treatment of patients with mild to moderate hypercholesterolemia:

TABLE 2. Dose-Response in Patients With Mild to Moderate Hypercholesterolemia (Mean Percent Change from Baseline)*

Lipid Parameter	LIPITOR Dose (mg/day)			
	10 (N=22)	20 (N=20)	40 (N=21)	80 (N=23)
Total-C: 7.1 mmol/L ^a (273 mg/dL) ^b	-29	-33	-37	-45
LDL-C: 4.9 mmol/L ^a (190 mg/dL) ^b	-39	-43	-50	-60

* Results are pooled from 2 dose-response studies

^b Mean baseline values

Severe Hypercholesterolemia

In patients with severe hypercholesterolemia, including heterozygous familial hypercholesterolemia, higher dosages (up to 80 mg/day) may be required (see WARNINGS, Pharmacokinetic Interactions, Muscle Effects and PRECAUTIONS, Drug Interactions).

Concomitant Therapy

See PRECAUTIONS, Drug Interactions.

Dosage in Patients With Renal Insufficiency

See PRECAUTIONS.

PHARMACEUTICAL INFORMATION

Drug Substance

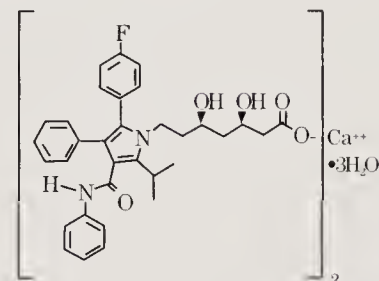
Proper Name: Atorvastatin calcium

Chemical Name: [R-(R*,R*)]-2-(4-fluorophenyl)-8, δ -dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino) carbonyl]-1H-pyrrole-1-heptanoic acid, calcium salt (2:1) trihydrate

Empirical Formula: (C₃₃H₃₄FN₂O₅)₂Ca • 3H₂O

Molecular Weight: 1209.42

Structural Formula:



Description: Atorvastatin calcium is a white to off-white crystalline powder that is practically insoluble in aqueous solutions of pH 4 and below. Atorvastatin calcium is very slightly soluble in distilled water, pH 7.4 phosphate buffer and acetonitrile, slightly soluble in ethanol, and freely soluble in methanol.

Tablet Composition: Each tablet contains either 10 mg, 20 mg or 40 mg atorvastatin as the active ingredient.

Each tablet also contains the following non-medicinal ingredients: calcium carbonate, candellilla wax, croscarmellose sodium, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, hydroxypropyl methylcellulose, polyethylene glycol, talc, titanium dioxide, polysorbate 80 and simethicone emulsion.

Stability and Storage Recommendations: Store at controlled room temperature 15 to 25°C.

AVAILABILITY OF DOSAGE FORMS

LIPITOR (atorvastatin calcium) is available in dosage strengths of 10 mg, 20 mg and 40 mg atorvastatin per tablet.

10 mg: White, elliptical, film-coated tablet, coded "10" on one side and "PO 155" on the other. Available in bottles of 90 tablets.

20 mg: White, elliptical, film-coated tablet, coded "20" on one side and "PO 156" on the other. Available in bottles of 90 tablets.

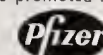
40 mg: White, elliptical, film-coated tablet, coded "40" on one side and "PO 157" on the other. Available in bottles of 90 tablets.

References:

1. LIPITOR (atorvastatin calcium) Product Monograph, Parke-Davis Div., Warner-Lambert Canada Inc., July 1998.
2. Dart A, Jerums G, *et al.* A multicenter, double-blind, one-year study comparing safety and efficacy of atorvastatin versus simvastatin in patients with hypercholesterolemia. *Am J Cardiol* 1997;80:39 - 44.
3. Bertolini S, Bittolo Bon G, *et al.* Efficacy and safety of atorvastatin compared to pravastatin in patients with hypercholesterolemia. *Atherosclerosis* 1997; 130:191-197.
4. Davidson M, McKenney J, Stein E, *et al.* Comparison of one-year efficacy and safety of atorvastatin versus lovastatin in primary hypercholesterolemia. *Am J Cardiol* 1997; 79:1475-1481.
5. Heinonen TM, *et al.* Atorvastatin, a new HMG-CoA reductase inhibitor as monotherapy and combined with colestipol. *J Cardiovasc Pharmacol Therapeut* 1996; 1(2):117-122.

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Risk Factors for Developing Osteoarthritis in the Anterior Cruciate Ligament-Deficient Knee: Future Role of the ACL Risk Equation

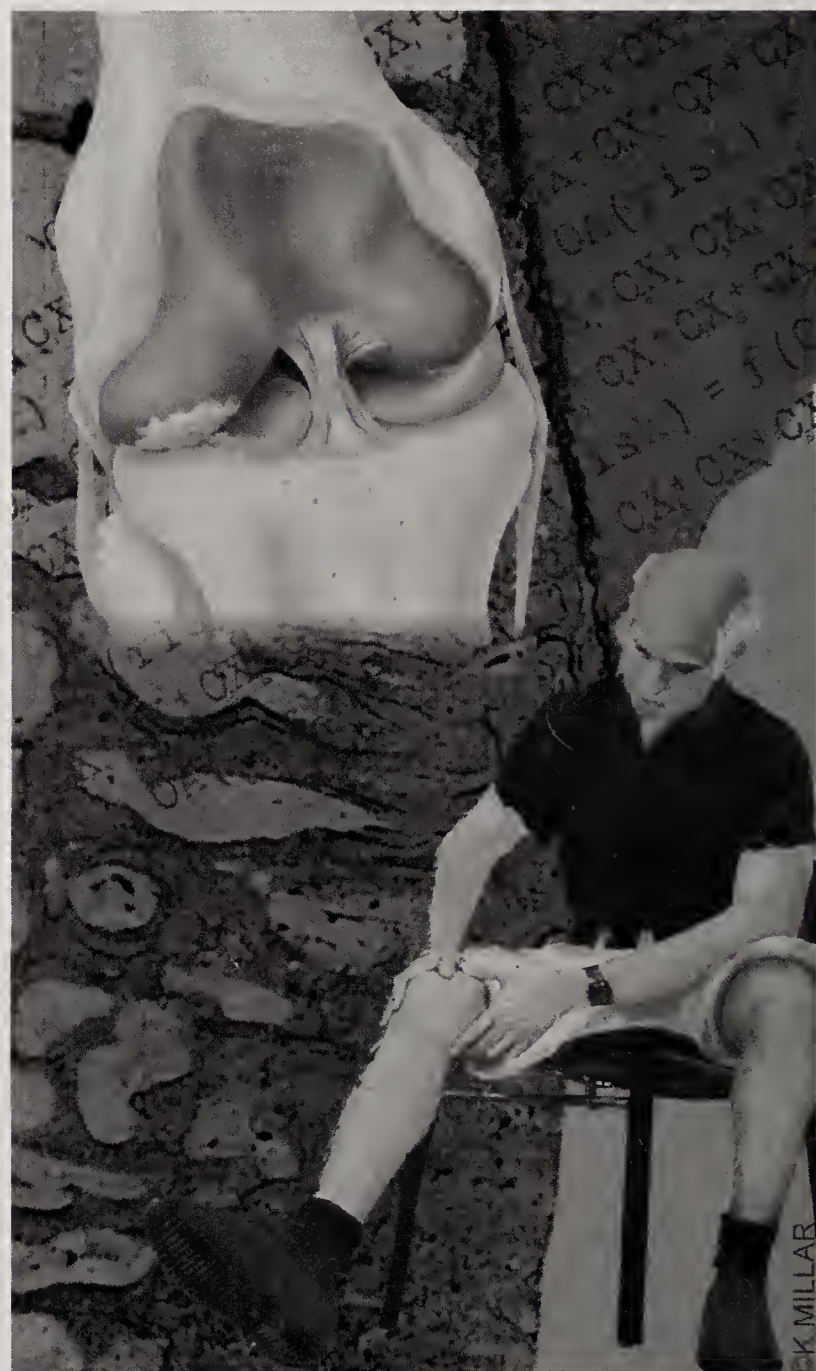
Kurt P. Droll, MSc. (OT0), and Paul H. Marks, BSc., MD, FRCSC*

Abstract

Osteoarthritis (OA) is found more commonly in the knee than in any other weightbearing joint in the human body. Individuals with anterior cruciate ligament (ACL) insufficiency have been found to have a significantly higher risk for developing OA in the knee compared to the general population. Several risk factors have been implicated in the development of OA in the ACL-deficient knee including concomitant meniscal pathology, osteochondral pathology, impaired proprioception, and an imbalance of biochemical mediators in the knee joint. The following article reviews the evidence pertaining to the above risk factors. In addition, in an effort to aid in the future prognosis of post-traumatic OA, we propose that an "ACL Risk Equation" be developed which would express overall OA risk quantitatively. This proposed equation would be a function of all the pertinent risk factors.

Introduction

Osteoarthritis (OA) is one of the most common diseases in the world, and it has been estimated that 10% of the general population of North America suffers from this disorder.^{1,2} This translates into approximately 2.7 million Canadians. Osteoarthritis, also known as degenerative joint disease, is found more commonly in the knee than in any other weightbearing joint in the human body.³ The principal pathologic features of this disease include progressive focal degradation of the articular cartilage, with subsequent joint space narrowing and formation of new bone in the floor of the cartilage lesion



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and at the joint margins (i.e. osteophytes).⁴ These structural changes in the knee can manifest clinically as joint pain, stiffness, crepitation, loss of motion, and enlargement.⁵ Consequently, OA in the knee joint may significantly impair lower extremity function and ambulation thus making it extremely disabling and detrimental to overall quality of life. For example, individuals with knee OA have been reported to be twice as likely as those free of OA to have limitations in physical functioning such as travelling up or down stairs or engaging in "heavy chores."⁶ From an economic perspective, it has been postulated that the annual cost of OA in Canada is 4 billion dollars,⁷ and since the knee is the most commonly affected site it is without a doubt responsible for a large proportion of this financial burden. As a result, OA of the knee joint is a major public health problem worldwide.

Despite OA of the knee being relatively prevalent in the population, the etiology and prognostic factors for this disease are poorly understood. However, several studies have implicated anterior cruciate ligament (ACL) insufficiency as a precursor for degenerative change in the knee.^{8,9,10,11} These studies reported that individuals with chronic ACL deficiency are at a significantly higher risk for developing OA as compared to the general population. Anterior cruciate ligament insufficiency is a relatively common condition. Nielsen and Yde¹² reported an ACL injury rate of 0.3 per 1,000 inhabitants in Denmark during a 1-year period among a community of 256,000 inhabitants (i.e. 76 ACL injuries). Another population based study from the San Diego Kaiser Health Plan evaluated knee injuries over a 3-year period among 280,000 inhabitants. The rate of ACL injury was reported to be 0.34 per 1,000 individuals.¹³ As expected, rupture of the ACL is a more common event in athletes. A large proportion of ACL ruptures occur while participating in sporting activities, principally those that involve deceleration, twisting, cutting, and jumping movements. In a study of ski injuries, Feagin and associates¹⁴ reported 72 ACL injuries per 100,000 skier days and estimated over 100,000 ACL injuries in the United States per year from skiing alone. In addition, a football injury study reported 42 ACL injuries per 1,000 players which extrapolated into a 16% chance of ACL injury in a 4-year collegiate career and a 100-fold increased risk for ACL injury compared with the general population.¹⁵ As reported in the Kaiser study, sporting activities such as football, baseball, soccer, basketball, and skiing accounted for approximately 78% of the ACL injuries sustained while participating in sports.¹³ Consequently, many individuals rupture their ACL each year which results in an increased likelihood of becoming disabled with OA in the future.

The natural history of the ACL-deficient knee has yet to be completely elucidated, therefore much debate exists regarding the relationship between osteoarthritis and the anterior cruciate ligament-deficient knee. In addition to pain and swelling,³⁹ previous studies have documented that ACL rupture often leads to joint instability.^{11,16} Consequently, this data has pro-

vided the impetus for many researchers to postulate that repetitive anterior tibial subluxation episodes under weightbearing conditions, can cause intraarticular damage to structures such as the articular cartilage, menisci, joint capsule and ligamentous restraints. Thus resulting in additive trauma and progressive deterioration of the joint and in turn, OA.¹⁷ Many researchers are convinced of this causal relationship such as Lynch and Henning¹⁸ who state that "degenerative arthritis in the ACL-deficient knee is inevitable." However, controversy surrounds this topic because several studies do not directly support this theory. Ferretti and associates¹⁹ and more recently, Daniel and associates²⁰ have reported that individuals who underwent ligament reconstruction acutely have an overall higher likelihood of developing arthrosis in that knee. This suggests that the etiology of the osteoarthritic changes seen after ACL rupture is multifactorial, and not solely due to biomechanical disturbances. Therefore, the purpose of this paper is to outline several risk factors which have been implicated to play a role in the development of OA in the ACL-deficient knee such as concomitant meniscal pathology, osteochondral pathology, impaired proprioception, and an imbalance of biochemical mediators in the knee joint.

Meniscal Pathology

Structure and Function of Normal Meniscus

The menisci are crescent shaped wedges of fibrocartilage located between the condyles of the femur and tibia (see Figure 1). These structures are composed primarily of Type I collagen (accounts for 90% of total collagen within meniscus), and other components which are found in much smaller quantities such as noncollagenous protein, proteoglycans, and interstitial fluid.²¹ The vascular supply of the menisci originates predominantly from the inferior and superior lateral and medial geniculate arteries. The degree of peripheral vascular penetration however, has been found to be only 10-30% of the outer width of the adult meniscus.²² Therefore, the majority of the meniscus is avascular which profoundly influences its ability to heal from injury. Several studies have shown that the menisci

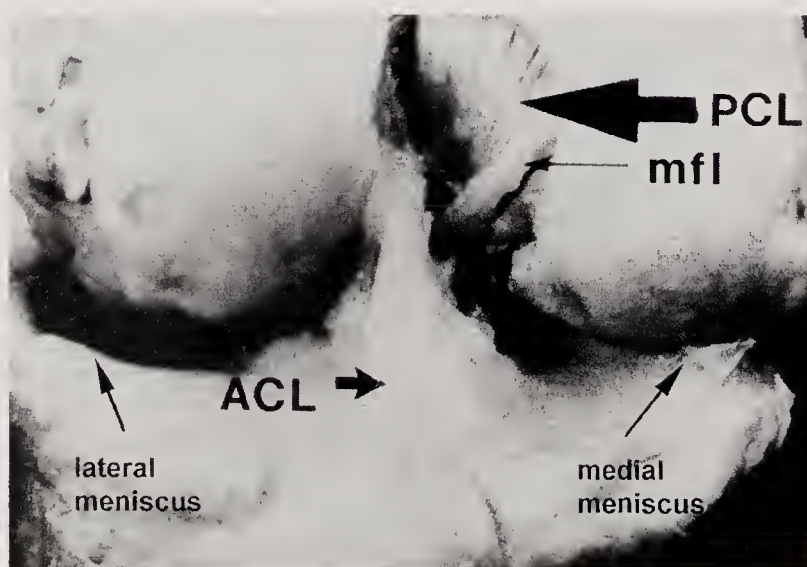


Figure 1. Anterior view of the right knee showing gross anatomy of the cruciate ligaments and menisci. ACL-Anterior Cruciate Ligament, PCL-Posterior Cruciate Ligament, mfl-meniscal femoral ligament of Humphrey's.

have a characteristic pattern of collagen fiber orientation. The majority of collagen fibers are aligned in a circumferential fashion, yet there are some that are oriented radially, particularly at the meniscal surfaces.^{23,24} Thus, the biomechanical functions of the meniscus stem from the physical properties of this matrix.

The menisci were for many years believed to be simply vestigial structures. However, a large body of evidence from the last few decades has suggested that the meniscus serves a variety of significant functions. Biomechanical studies have established that the meniscus has an important role as a load-bearing structure, for it has been reported that 50% to 85% of the compressive load of the knee joint is transmitted through the meniscus.²⁴ In addition, the viscoelastic properties of menisci allow them to function as shock absorbers in dampening the load generated during weight-bearing activity.²⁵ As a result, intact menisci transmit load and absorb energy, thus protecting the articular surfaces from compressive stress. In the kinematics of a normal knee, there is both sliding and rolling motion of the femur on the tibia. This is accomplished by articulating a rounded femoral condyle with a relatively flattened tibial plateau. As a result, only a small region of the femur is in direct contact with the tibia. Therefore, the menisci decrease joint incongruity by filling in the space between the tibia and the femur.²⁶ By increasing joint congruity, the menisci are able to assist in joint stability by deepening the articular surfaces of the tibial plateau.²⁷ This is particularly relevant in the ACL-deficient knee, for Levy and associates²⁸ showed that the posterior horn of the medial meniscus acts as a posterior wedge, and thus serves as a secondary restraint to anterior tibial translation. Furthermore, during joint motion the menisci contribute to joint lubrication by spreading synovial fluid over the articular surfaces, and during weight-bearing serve to compress nutrients into the articular cartilage.²⁹

Prevalence and Pattern of Meniscal Injury in ACL-Deficient Knees

Anterior cruciate ligament-insufficiency is associated with a high rate of concomitant meniscal lesions. In acute ACL-deficiency, the incidence of meniscal tears has been reported to range from 41% to 77%.³⁰⁻³⁶ In contrast, the reported rate of meniscal injury in intact ACL knees is 15% to 25%.^{30,31} In the chronic ACL-deficient knee, the incidence of meniscal damage is reported to be even higher, with rates ranging from 73%-98%.^{33,37-40} Woods and Chapman³² compared a group of patients with chronic injuries to a group with acute injuries and reported that the incidence of meniscal tears almost doubled (88% vs. 45% respectively). Therefore, some meniscal injuries occur at the time of initial injury, while others may result from recurrent giving way episodes long after the ACL was disrupted.

The incidence of medial versus lateral meniscal injuries has been described. While the type of injury is obviously influenced by the mechanism of injury, lateral meniscal tears are more common in acute ACL ruptures,^{40,41} and medial tears predominate with

chronic insufficiency.^{32,33} Thus indicating continued injury to the medial meniscus over time due to knee instability. In the chronic setting, MacIntosh has called the ACL the "watchdog of the medial meniscus" (personal communication). In both situations of acute and chronic ACL-deficiency, the peripheral posterior horns of the meniscus are at greatest risk of tearing and account for more than half of the meniscal injuries identified.⁴² However, differences in the type of meniscal tear are evident depending upon whether it is located in the medial or lateral meniscus. A peripheral longitudinal tear is the most common medial meniscal lesion, while the lateral meniscus is more at risk for a radial tear.⁴³ The type of meniscal tear and its association with osteoarthritis will be discussed subsequently.

Meniscal Pathology and Osteoarthritis of the ACL-Deficient Knee

The role of meniscal lesions in the pathogenesis of OA in the knee continues to be the focus of considerable discussion. Loss or damage of this structure has been associated with an accelerated development of OA.^{38,44,45} Fairbank in his classic paper from 1948,⁴⁴ described postmeniscectomy (i.e. removal of meniscus) roentgenographic changes that included joint space narrowing, osteophyte development, and flattening of the femoral articular surface. He reported these changes were present in 50% to 66% of the knees studied after meniscectomy, but were observed in only 5% of the contralateral knees. Consequently, he was one of the first to postulate that loss of the load-bearing role of the meniscus leads to degenerative changes. An example of roentgenographic degenerative change of the knee is presented in Figure 2.



Figure 2. Plain radiograph of the knee demonstrating severe degenerative disease in the medial compartment.

The importance of an intact meniscus in the prevention of OA in an ACL-deficient knee has been well documented. Sherman and associates⁸ reported a significantly higher incidence of degenerative change in ACL-insufficient knees with prior meniscectomy compared to those without meniscectomy. This is in agreement with the findings of several authors.^{18,39,46} Furthermore, individuals who had both menisci removed were reported to have a higher frequency of OA than individuals with unilateral meniscectomy or meniscal repair.⁴⁶ In addition, Sommerlath and Gillquist⁴⁷ found that in a 7-year follow-up of subjects with intact ligaments, degenerative arthritis occurs more frequently in patients with total meniscectomy than in those with only partial meniscectomy.

Meniscectomy has been shown to profoundly affect the manner in which load-bearing occurs in the knee joint. As a result of partial or total meniscectomy the contact area between the tibia and femur is decreased by approximately 30% to 50%.⁴⁸ Consequently, the reduced contact area increases the stresses of compression and shear across the articular cartilage likely resulting in degenerative change.⁴⁹

The progression of articular degeneration in the knee can also be influenced simply by having a meniscal injury (without a history of meniscectomy). Satku and associates⁴⁵ reported that all ACL-deficient subjects with clinical evidence of meniscal injury but no meniscectomy had degenerative change in the knee. However, not all meniscal tears are associated with damage of the articular cartilage. Unstable tears, such as bucket-handle, longitudinal with broken handles, and complex tears have been shown to correlate with an increased incidence of OA.^{18,50} Figure 3 illustrates a classic bucket-handle tear of the meniscus. Nevertheless, it has been demonstrated that damaged menisci still distribute some load and these knees are less likely to have OA complications than those knees treated with partial or total meniscectomy.^{51,52} Consequently, the risk of degeneration

appears to be influenced by the degree of meniscal pathology and as a result, the primary goal of management is to preserve the meniscus if at all possible.

Osteochondral Pathology

Prevalence and Pattern of Osteochondral Pathology in ACL-Deficient Knees

The increasing utilization of magnetic resonance imaging (MRI) and arthroscopy in the management of musculoskeletal trauma have allowed investigators to reliably identify lesions of articular cartilage and bone within the knee joint.^{53,54,107} These lesions were previously not visualized on routine roentgenograms. An acute rupture of the ACL has been shown to be associated with damage to both these structures in the knee.^{55,56}

The reported incidence of chondral injury in the acutely ruptured ACL knee ranges from 18% to 46%.^{20,52,55,56,57,58} These studies commonly defined articular cartilage injuries as any chondromalacia, fractures, impaction, creases, or fissures upon observation; an example of which can be seen in Figure 4. Furthermore, the medial compartment has been reported to be more at risk of sustaining damage than the lateral compartment.^{20,34} However, the two studies which analyzed the location of the chondral injury did so three months after the injury. Therefore, it is possible that these studies did not accurately document articular damage at the time of injury but rather, subsequent damage due to altered pathomechanics (i.e. giving out episodes) of the ACL-deficient knee.

In 1989, Mink and Deutsch⁵⁹ coined the term "bone bruise" to describe post-traumatic subcortical regions of altered signal intensity in the femur and/or tibia on T1- and T2-weighted MR images. The lesions on T1-weighted images are characterized by a decreased signal intensity while on T2-weighted images there is a corresponding increase in signal intensity (see

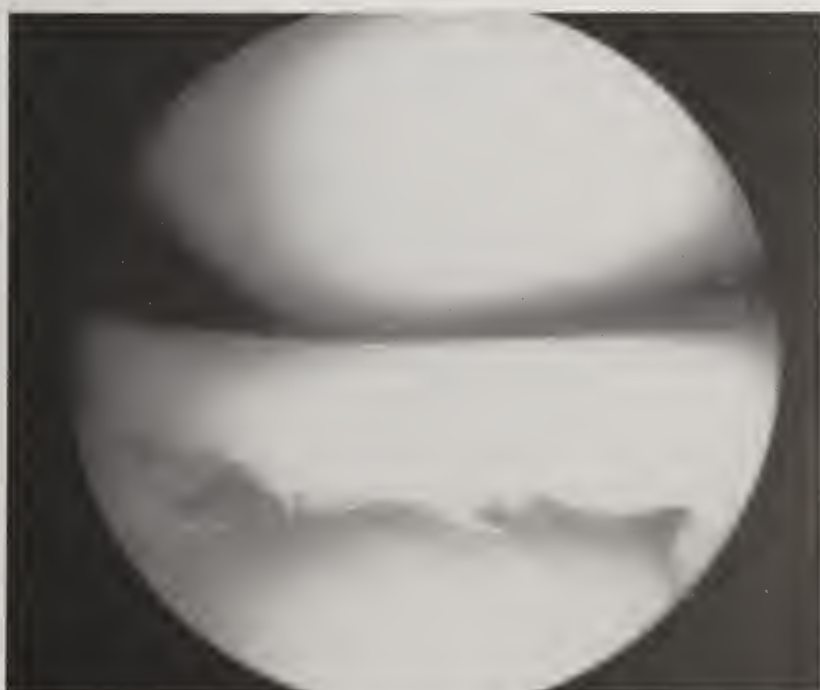


Figure 3. Arthroscopic view of the knee revealing a displaced "bucket-handle" medial meniscal tear.

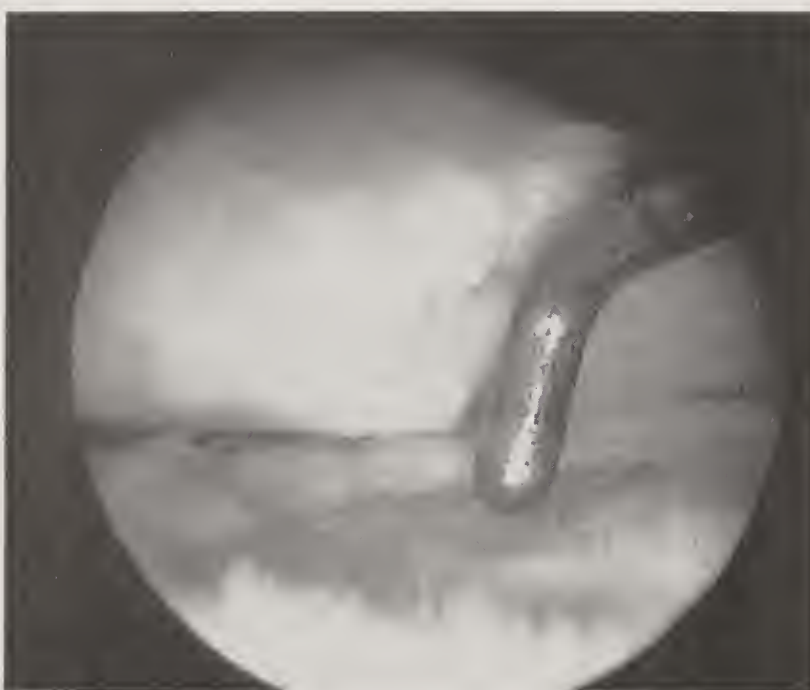


Figure 4. Arthroscopic view of the knee demonstrating severe degenerative disease down to eburnated bone on the tibial surface.

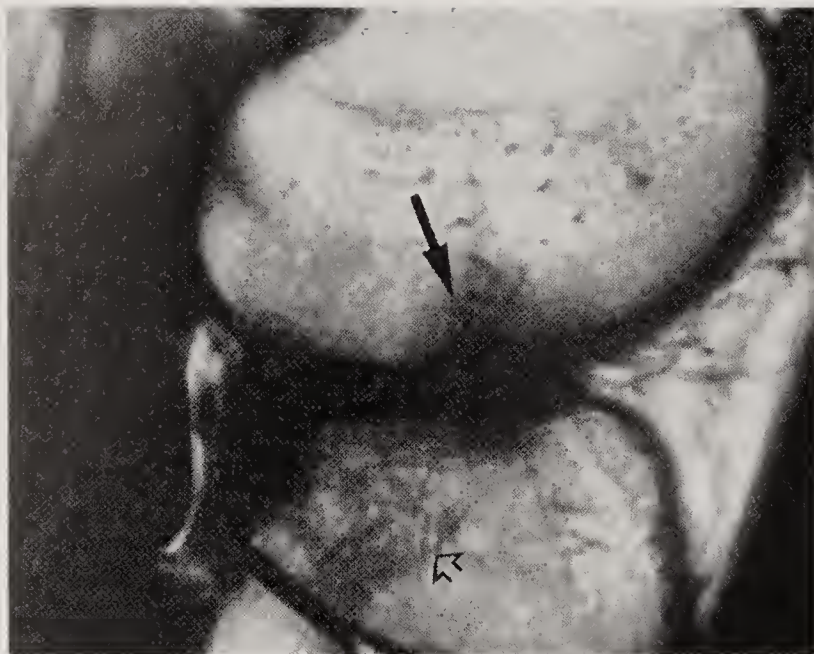


Figure 5. T1-weighted magnetic resonance image showing sites of osseous injury of the anterior aspect of the lateral femoral condyle (closed arrow) and the posterior aspect of the lateral tibial plateau (open arrow).

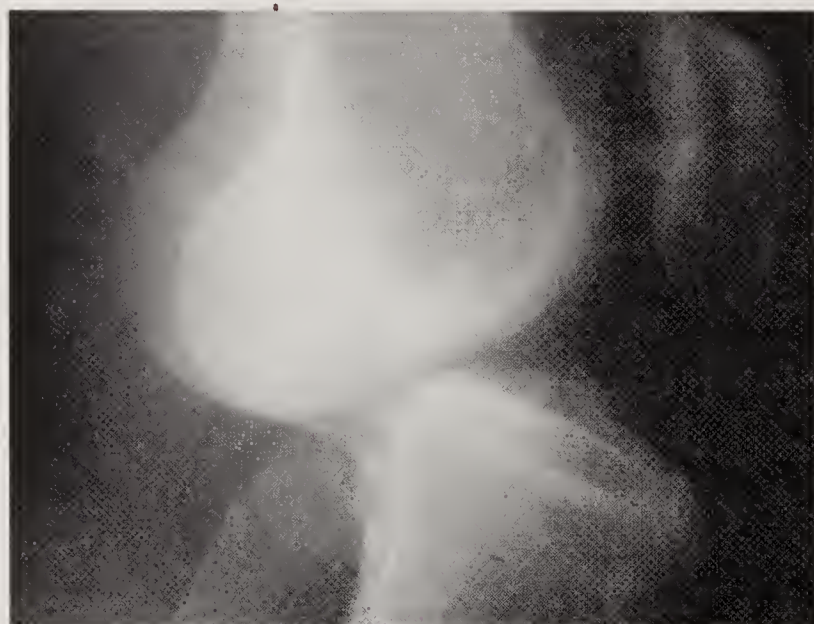


Figure 6. Image of the knee in a patient who had an acute rupture of the anterior cruciate ligament. This lateral view demonstrates the impact of the lateral femoral condyle on the posterior aspect of the lateral tibial plateau.

Figure 5). These “bone bruises” were subsequently classified by Vellet and colleagues⁵³ according to their architectural appearance, their spatial relationship with cortical bone, and their short-term osteochondral sequelae. There is general agreement that the pathogenesis of these identifiable lesions on MRI result from microtrabecular fracture. This bone injury and its sequelae, i.e. hemorrhage, edema, and inflammation, are responsible for the abnormal signals seen on imaging.⁵⁹ The reported incidence of bone bruises with acute ACL rupture is even higher than that observed for articular cartilage injury. Several studies have revealed that approximately 80% of patients with a complete tear of their ACL have concomitant bone bruises.^{53,58,60,61} Bone bruises are evident in many sites within the knee joint, however, approximately 80% occur in the lateral compartment.^{58,62} The sulcus terminalis of the lateral femoral condyle and the posterior tibial plateau are the most common areas involved. The high frequency of bone bruises

in the lateral compartment of an acute ACL-deficient knee suggests that the mechanism of injury includes anterior subluxation, increased internal rotation of the tibia, and a valgus stress. This would position the lateral femoral condyle over the posterior edge of the lateral tibial plateau as seen in Figure 6. With subsequent valgus stress, impaction of these structures occurs resulting in localized osseous contusions.⁶⁰ In addition, bone scintigraphy has confirmed the location and presence of bone bruises in acute ligamentous knee injuries.¹⁰⁵

Osteochondral Pathology and Osteoarthritis of the ACL-Deficient Knee

Direct chondral injuries such as those identified by arthroscopy have been shown to initiate the process of OA.⁶³ This has been postulated to occur due to the limited ability of articular cartilage to repair itself. The impaired ability to heal stems from the lack of blood supply and also from the inability of articular cartilage chondrocytes to form adequate new tissue.⁶⁴ The severity of chondral injury appears to play a role in the progression of OA, as demonstrated by animal model studies. Injuries graded as “superficial” may cause death of cells surrounding the injury, however, they do not necessarily lead to OA unless there is accompanying joint incongruity.⁶³ Deep penetrating injuries on the other hand heal inadequately, for the defect fills in with cartilaginous tissue that is not articular cartilage but rather a mixture of hyaline and fibrocartilage. Consequently, this new tissue does not remain intact over time and thus contributes to the future development of cartilage degeneration.⁶⁵ With regards to the ACL-deficient knee, repeated episodes of anterior subluxation can exacerbate existing articular cartilage damage.⁶⁶ Thus, the chondral lesion accompanying the acute rupture of the ACL may provide a focus for deterioration of the articular cartilage.

The natural history of bone bruises and their pathodegenerative implications within the knee joint remains largely unknown. Bone bruises represent a blunt injury to the overlying articular cartilage, subchondral bone, and inner marrow. Because of their relatively high occurrence in acute ACL injuries they have generated a renewed interest in the etiology of post-traumatic knee OA. A number of recent animal model studies have investigated this possible relationship. Mankin⁶⁶ reported that a single, supraphysiological blow to the surface of canine knee articular cartilage which exceeds a critical threshold serves as a precursor for OA. Whether the trauma experienced at the time of ACL trauma is significant enough to exceed this threshold remains unknown. Donohue and associates⁶⁷ have noted that blunt trauma to adult canine articular cartilage produces changes in its histological, biochemical, and ultrastructural characteristics without articular surface disruption. In addition, they showed that it may be weeks or months before surface abnormalities become apparent. Consequently, the articular cartilage could be damaged yet appear normal on arthroscopic evaluation immediately following injury and degenerative change may not become visibly apparent until

much later. This is consistent with clinical results reported by Graf and associates⁶² and Mink and Deutsch⁵⁹ who stated that there was no correlation between the location of bone bruises on MRI and articular cartilage damage in acute ACL-deficient knees.

There is a lack of data concerning this topic from human studies in the literature, however, Vellet and associates⁵³ prospectively studied bone bruises and acute ACL tears. They reported that bone bruises localized in the medullary area (i.e. reticular) resolved completely within 3 months, however, lesions characterized by their contiguity with the subadjacent cortical bone (i.e. geographic) had evidence of osteochondral sequelae at follow-up 6-12 months later. These changes included subcortical sclerosis, cartilage thinning, cartilage loss, and cortical impaction. Coen and associates⁶⁸ have recently reported a phenomenon they have termed "dimpling" which describes a softening of articular cartilage overlying an occult osseous injury. The cartilage transiently indents after gentle placement of a probe. The long-term sequelae of dimpling is unknown. However, it may prove to be an early prognostic indicator of OA. Researchers have postulated that the mechanism for post-traumatic OA from a bone bruise is that the subchondral bone heals via callous formation resulting in a stiffer construct than the previous normal bone. The decreased compliance of the new subchondral bone would require the articular cartilage to absorb more of the compressive forces and thus possibly lead to degenerative change.⁶¹ The minimal evidence published to date nevertheless indicates that blunt trauma to the articular cartilage, even when not visible on initial inspection, may have profound effects on future cartilage integrity.

Impaired Proprioception

Proprioception in the Normal Knee

Recently, it has become apparent that most intraarticular and periarticular knee joint structures, in addition to their mechanical function, also play an important role in knee proprioception.^{69,70} Proprioception is considered a specialized variation of the sensory modality of touch and encompasses the sensations of joint movement (i.e. kinesthesia) and position (i.e. joint position sense).⁷¹ Proprioception in the knee has been shown to be provided by mechanoreceptors localized in the muscle, tendon, skin, capsule and ligaments.^{69,70} Recent neuroanatomical studies have demonstrated specialized mechanoreceptors such as Ruffini endings, Golgi tendon organs, and Pacinian corpuscles in the human ACL.⁷² These mechanoreceptors respond to mechanical deformation (e.g. tension) of the tissue and serve to translate the stimulus into specific neuronal signal(s).⁷² They have been found to be more active at the extreme ranges of motion and are also responsible for initiating reflex contraction about the knee joint; both these properties may serve a protective or stabilizing role.^{69,74} Consequently, the ACL provides important neurologic feedback to the central nervous system which directly mediates joint position sense and protective

muscular stabilization reflexes about the joint.^{73,74} Therefore, a lack of afferent input from these mechanoreceptors may contribute to the progressive functional decline of the knee joint.

Impaired Proprioception and Osteoarthritis in the ACL-Deficient Knee

A significant deterioration in the proprioception of knee joints with an ACL rupture compared to the non-injured contralateral knee joint or an age-matched control group has been well documented by several investigators.⁷⁵⁻⁷⁹ As mentioned previously, complete ACL insufficiency and thus loss of this ligament's mechanical function, creates an unstable knee. Loss of ACL proprioceptive function, as originally proposed by Kennedy and associates,⁶⁹ is thought to contribute to this increasing instability over time through loss of the dynamic stabilizing reflexes. If this were the case, then proprioceptive loss would be expected to be present acutely as well as chronically. If loss of the ACL simply results in loss of passive restraint, which over time leads to mechanical stretching of capsular structures and a possible change in response of capsular receptors, then a chronic, but not acute, loss of proprioception would be expected. Barrack and associates⁷⁵ and MacDonald and associates⁷⁶ showed no difference in proprioception deficits between knees with acute and chronic injuries. Thus suggesting that proprioceptive loss can also be a cause of increased joint laxity and not just the result of it.

Appropriately coordinated and timed muscle coactivation normally attenuates load across the articular cartilage. Muscle activity is a critical determinant of the mechanical stiffness of the joint, which relates to its ability to resist disturbances and to maintain articular congruence.⁸⁰ Afferent signals from mechanoreceptors in the ACL have been shown to initiate joint-protective muscular reflexes. Joint instability occurs when there is a lack of muscular reflex stabilization. Researchers have established that the lack of reflex stabilization of the knee is associated with a diminished sensory feedback mechanism, which causes a latent motor response of the hamstring muscles. Beard and associates⁷⁸ reported in 1993 that reflex hamstring contraction latency is significantly slower in ACL-deficient knees than in the contralateral non-injured knee. Furthermore, they claimed the greater the latency, the greater the instability. This data suggested that the loss of proprioceptive input from the ruptured ACL, evident as the longer response time required for the ACL-hamstring reflex arc to become active, contributes significantly to the functional instability of the knee. This corroborates with Kennedy's original theory.

The relationship between impaired proprioception and osteoarthritis has been minimally evaluated. Barrett and associates⁸¹ reported that joint position sense was impaired in a cohort of patients with osteoarthritic knees. However, this was not a longitudinal study and therefore it is difficult to conclude whether the loss of position sense causes OA, is a consequence of it, or both. Many osteoarthritic patients have an abnormal

wide-based gait but it may not necessarily be related to the pain experienced. Instead it may be due to the loss of proprioception. The abnormal gait has been proposed by some authors to result from an effort to maximize proprioceptive input.^{81,82} A similar effect is observed in the ACL-deficient knee. The gait of a patient with an ACL-deficient knee is designed to prevent excessive anterior displacement of the tibia, and is reported to result from abnormal proprioception.^{79,83} After an ACL rupture, proprioception must arise from other intact structures within the knee joint. However, the ACL-deficient knee has been shown to move in a non-physiological axis,⁸³ implying that the remaining proprioceptive output is non-physiological and disorganized. Consequently, patients feel the knee to be unstable because cortical interpretation and analysis of knee position is disturbed. Therefore, the lack of proprioceptive feedback resulting from a rupture of the ACL leads to poor spatial and temporal coordination of muscle activity and limb position. This is characterized clinically by joint instability and an abnormal gait. As a result, this causes an increased, repetitive, poorly distributed load across the joint surface which leads to progressive degenerative change in the knee.^{79,84} Longitudinal studies are required in order to fully elucidate the relationship between impaired proprioception and OA in ACL-deficient knees.

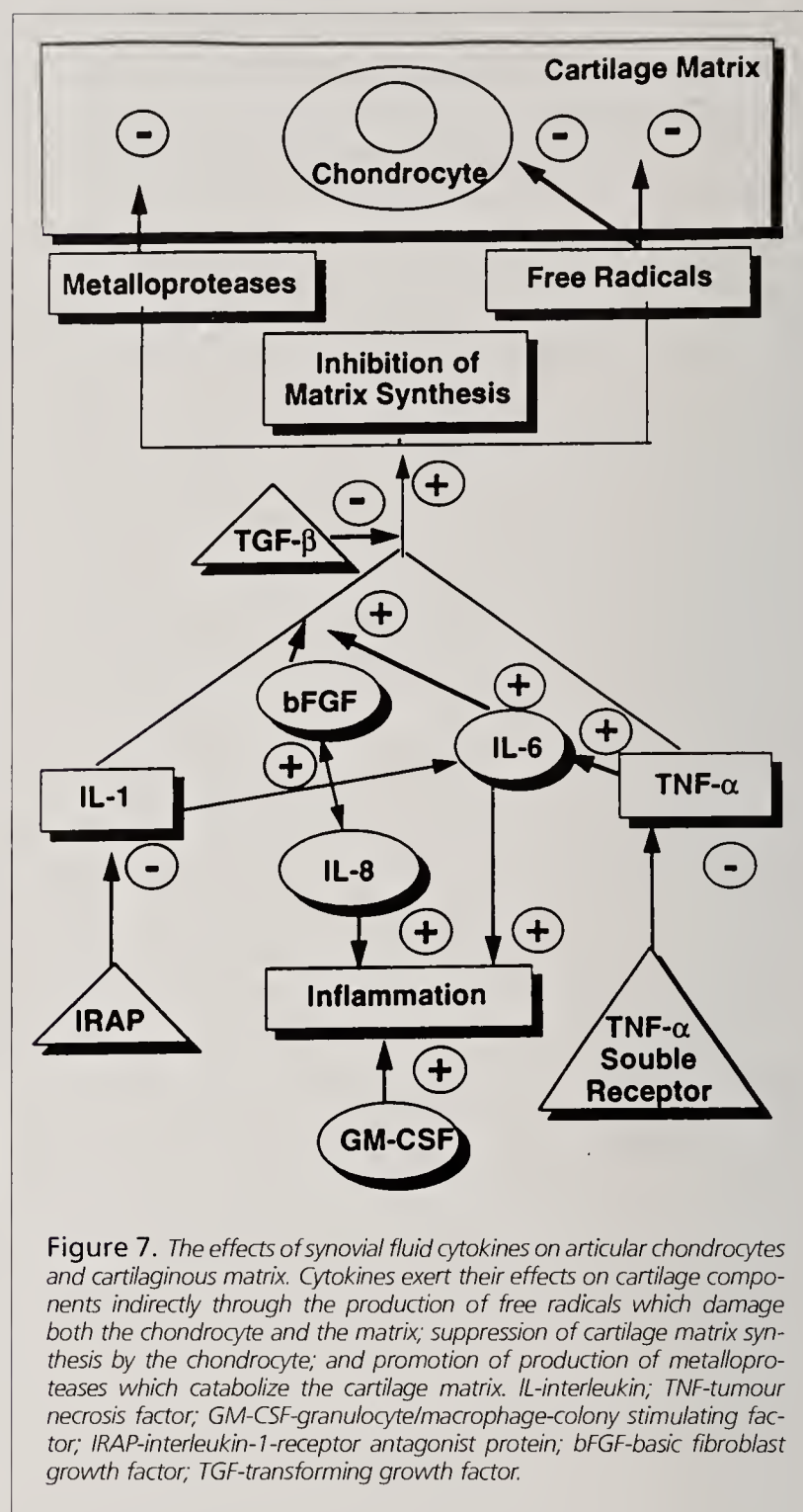
Biochemical Mediators

Biochemistry of Articular Cartilage

Articular cartilage is a highly differentiated tissue consisting of four major components: chondrocytes, Type II collagen, proteoglycan, and water. The three latter components form the extracellular matrix (ECM) of the cartilage, the conformation of which provides the property of resilience. As a result, the articular cartilage located in the knee joint is able to resist load-bearing forces.⁸⁵ Chondrocytes, although few in number, play a key role in matrix homeostasis. Matrix integrity is maintained through the regulation of degradative and synthetic events. This regulation is mediated by biological agents known as cytokines. Cytokines are polypeptides released by living cells which act as local intercellular messengers to regulate host cell function.¹⁰⁶ Specifically, catabolic cytokines act on chondrocytes and synovial cells to induce production of matrix degrading enzymes, such as metalloproteases. This is normally balanced by anabolic cytokines which act on chondrocytes to induce production of cartilage matrix.⁸⁶ This process is schematically outlined in Figure 7. Alterations in the concentrations of any of the components responsible for this homeostasis may shift the equilibrium in favor of either overproduction of matrix proteins or to net degradation.

Biochemical Mediators of OA in an ACL-Deficient Knee

The reported frequency of post-traumatic OA following ACL injury has been rather variable. This has led researchers to postulate that endogenous factors, in addition to mechanical factors, contribute to the development of knee OA. Osteoarthritis is characterized by slow changes in matrix



metabolism. Initially there is an increase in the water content of cartilage implying a failure in the elastic restraint of the collagen network. Shortly afterward, an increased turnover of proteoglycans occurs followed by an eventual net loss of proteoglycans from the ECM as catabolic events dominate over anabolic events.^{87,88} Therefore, an imbalance between the anabolic and catabolic events occurs in OA, resulting in the loss of cartilage matrix. The role of cytokines in this process has received particular attention due to their function, as described above, in regulating articular cartilage matrix homeostasis. The intraarticular cytokines most commonly implicated in the pathogenesis of OA have been interleukin (IL)-1, 6, and 8, interleukin-1-receptor antagonist protein (IL-1Ra), tumour necrosis factor alpha (TNF- α), and granulocyte/macrophage-colony stimulating factor (GM-CSF).

Interleukin-1 exists in two isoforms- alpha (α) and beta (β), and they both have the biological ability to suppress the syn-

thesis of Type II collagen which is a major constituent of articular cartilage matrix.⁸⁹ Furthermore, IL-1 promotes the resorption of the cartilage matrix by inducing the production of specific matrix degrading enzymes known as metalloproteases.⁹⁰ IL-1 also stimulates chondrocytes and synoviocytes to produce IL-6 which is believed to act as a co-factor for the inhibition of proteoglycan synthesis by IL-1.⁹¹ The cytokine IL-1Ra has been shown to antagonize the activity of both isoforms of IL-1.⁹² This is accomplished because IL-1Ra is a specific antagonist that competitively inhibits binding of IL-1 to its receptors. IL-1Ra is further characterized as having no intrinsic agonist activity.⁹³ Consequently, IL-1Ra can neutralize the catabolic effects of IL-1 α and IL-1 β .

The actions of TNF- α are very similar to those observed with IL-1. Tumour necrosis factor-alpha is a macrophage derived cytokine that also promotes the degradation of cartilage, and suppresses the synthesis of cartilage proteoglycans.⁹⁴ Like IL-1, TNF- α stimulates the secretion of IL-6 from chondrocytes. Furthermore, increased synthesis of IL-1 and metalloprotease has been shown to result from the actions of TNF- α .⁹⁰ Consequently, TNF- α and IL-1 provoke direct chondrodestructive effects as observed in the OA process. Interleukin-6, 8, and GM-CSF have been shown to promote intraarticular inflammation, which results in the production of more IL-1 and TNF- α .^{95, 96, 97} Therefore, these latter cytokines induce cartilage degradation indirectly via their inflammatory properties.

Only recently have researchers investigated the role of intraarticular cytokines in the pathogenesis of post-traumatic OA. Several researchers have reported that IL-1 α levels do not change in acute or chronic ACL-deficient knees compared to uninjured knees.^{98,99,100} However, levels of IL-1 β have been shown to increase after an acute ACL injury and they remain elevated, approximately four-fold when compared to uninjured knees, in the chronic setting.¹⁰⁰ The level of chondroprotective IL-1Ra is also increased acutely, however, there is only a slight increase, if at all, observed in chronic knees.^{98,99,100} This suggests the loss of an important chondroprotective cytokine in subjects with chronic ACL-deficiency. The chronic absence of IL-1Ra may allow IL-1 to act unabated and thus inflict more damage to the articular cartilage. Increased expression of IL-1 receptors on OA chondrocytes suggests that only small amounts of IL-1 α or β , such as those levels seen normally, are needed to trigger catabolic enzyme production in OA joints.¹⁰¹ The level of TNF- α has been reported to increase acutely and while its level falls over several weeks it remains elevated compared to uninjured knee values.^{98,99,100} This suggests that TNF- α may play a role in chronic cartilage loss after ACL rupture. High levels of IL-6 and 8 have been noted in the acute phase of ACL injury but they have been shown to fall back to the normal range by 3 months after injury. Conversely, the concentration of GM-CSF has been shown to remain near the normal range acutely, however, levels are elevated in the chronic setting.⁹⁹ This suggests that IL-6 and 8 play a role in acute inflammation while

GM-CSF assists in propagating chronic chondral destruction. Recent work by Marks and Cameron¹⁰⁰ demonstrated increased expression of IL-1 β and TNF- α with increasing grades of chondrosis in a chronic ACL-deficient knee. Furthermore, they showed decreasing IL-1Ra levels with increasing grades of chondrosis. This suggests that certain cytokine profiles are associated with greater risk for developing post-traumatic OA in the ACL-deficient knee.

Summary and Future Work

The etiology of degenerative change in the knee following rupture of the ACL remains uncertain. The development of OA in the ACL-deficient knee is a complex process with many factors likely contributing to its initiation and/or perpetuation. The role of biomechanical, neuroanatomical, and biochemical factors in the development of knee OA was the focus of this paper. Along with instability of the knee, the degree of meniscal pathology has been well established as having a profound influence on modifying OA risk. Of all the meniscal pathologies, meniscectomy, partial or total, appears to present the greatest OA risk, more so than damaged or repaired menisci. The magnitude of risk is illustrated by the fact that if a meniscectomy is performed, the development of OA is independent of the stabilization achieved with ACL reconstruction.¹⁹ Consequently, preservation of the meniscus should be a primary goal of management. Occult osseous lesions or bone bruises represent traumatic injuries to bone. They occur in more than 80% of individuals with complete ruptures of the ACL, and have been shown to have degenerative osteochondral sequelae. Therefore, MRI detected bone bruises are an important variable to consider. In addition, an ACL-insufficient knee has been shown to have deficits in proprioceptive function. This results in alterations in gait with resulting modifications in weight-bearing loads in the knee joint, which may lead to degenerative changes. The role of cytokines in promoting cartilage degradation has recently received attention. Individuals with relatively high concentrations of chondrodestructive cytokines, such as IL-1 β and TNF- α , and correspondingly low levels of chondroprotective cytokines such as IL-1Ra are at increased risk for developing post-traumatic OA in the ACL-deficient knee.

An important aspect to understand is that all the risk factors mentioned above do not act in isolation, but rather interact with each other to produce the degenerative changes. Moreover, other endogenous factors such as increasing age (>60),¹⁰² obesity,¹⁸ abnormal alignment of the knee joint,¹⁰³ genetic predisposition,¹⁰⁴ and high levels of activity,¹⁸ although not profiled in this paper, have also been implicated as risk factors for knee OA. Therefore, many factors may contribute to OA and orthopaedic surgeons need to be aware of all the possible risks in order to determine the proper prognosis for OA after ACL rupture. Consequently, in an effort to aid in the future prognosis of post-traumatic OA, we propose that an "ACL Risk Equation" be developed which would express

overall osteoarthritis risk quantitatively. This proposed equation would be a function of all the pertinent risk factors (see Figure 8). To properly generate the ACL Risk Equation, a multiple-variable analysis investigating the degree of interaction among these risk factors (which ultimately produce post-traumatic OA) is necessary. The ability to determine an individual's level of OA risk would aid the surgeon in tailoring pre- and post-operative management. In addition, novel therapeutic strategies may be subsequently developed, such as gene therapy, in order to counteract or neutralize the relevant factors and thus protect the ACL-insufficient knee from degenerative changes.

$$OA(risk) = f(C_1X_1 + C_2X_2 + C_3X_3 + C_4X_4 + C_5X_5 + C_6X_6 \dots)$$

C = Risk coefficient

X₁ = ACL instability

X₂ = Meniscal pathology

X₃ = Bone bruise (MRI)

X₄ = Cytokine abnormalities

X₅ = Impaired proprioception

X₆ = Other

Figure 8. Proposed ACL Risk Equation. OA risk as a function of documented risk factors.

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Huntington's Disease: Bridging Clinical and Basic Neurobiology

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Abstract

Huntington's disease (HD) is one of several neurodegenerative conditions produced by an expansion of a polyglutamine-encoding CAG-repeat within specific genes. In HD, the huntingtin protein possesses an elongated polyglutamine tract at its amino-terminal. The clinical profile of HD is characterized by mid-life development of progressive dyskinesia and mental decline, with death usually occurring 10-15 years after the onset of symptoms. While the genetic mutation that causes HD has been identified, the pathogenic role of the aberrant protein remains unclear. The last decade has seen great strides made in understanding this disease, with the last five years being particularly remarkable. The goal of this review is to provide a semi-comprehensive discussion of the current state of knowledge of HD with respect to clinical symptomatology, neuropathology and molecular neurobiology.

Introduction

Huntington's disease (HD) is a hereditary, neurodegenerative disorder with an autosomal dominant pattern of transmission and complete penetrance. It is characterized by cognitive, motor and psychiatric manifestations that cause progressive deterioration of an individual's quality of life, culminating in death 10-15 years after the onset of symptoms.¹ Onset of HD typically occurs in mid-life, but there is a juvenile form of the disease that strikes before the age of 20. The prevalence of HD varies among regions, but studies have estimated that it occurs between 5-8 per 100,000 in North America.^{2,3} To date, there is no cure for HD and pharmacological treatment, when available, is generally symptom-based and palliative in nature.

In the past decade, biomedical research has made enormous strides in developing the understanding of HD. Since the HD gene was identified in 1993, the genetic mutation that produces the pathogenic protein product has been determined. Huntington's disease is one of a growing number of neurological diseases whose etiology has been linked to an expansion of a CAG (glutamine-encoding)-repeat region in specific genes. Current efforts in HD research are focused on determining the pathogenic mechanisms that are induced by lengthened polyglutamine repeats in the brain, as well as understanding the link between the genetic/cellular pathology and the clinical symptomatology. Finally, understanding the role of the native HD protein in normal cellular physiology may provide clues to prospective therapeutic strategies for treating this disease.

Motor Abnormalities

The motor abnormality that is most commonly associated with HD is chorea. The involuntary muscle contractions are frequently observed in adult-onset HD, but rarely in the juvenile form, and typically involve the limb, trunk and facial muscles. The severity of chorea can vary from imperceptible twitching or fidgeting of the fingers to violent, uncontrollable flailing of the limbs. Often the patient may suppress initial choreiform activity, but as the disease progresses the motor abnormalities worsen and become uncontrollable. In addition to trunk and peripheral limb muscles, those of the pharynx may also be affected and result in speech difficulties (dysarthria) and the production of grunting or clucking sounds from forced air from the respiratory tract being pushed against a partially closed glottis.⁴

As the course of the disease progresses, the chorea observed in the early stages of adult-onset HD is often replaced, or masked, by rigidity and bradykinesia. These motor difficulties are also characteristic of juvenile HD. Bradykinesia and chorea have also been reported to occur simultaneously (although infrequently) in early-stage adult HD.⁵ Another motor abnormality frequently seen in advanced HD is dystonia, which may produce contortions of the face, limbs or trunk into characteristic postures. Additionally, irregularities in gait are frequently observed, such that individuals will walk with a wide-based, staggering gait, which may be misinterpreted as intoxication.⁶ Also, patients with HD often have difficulties performing normal eye movements, which typically worsen as the pathology progresses. Common ocular problems include saccade initiation,⁷ decrease in saccade velocity⁸ and accuracy^{7,9} and gaze fixation.⁸ Other motor problems that occur less frequently in adult-onset HD, but are common in juvenile HD include cerebellar dysfunction, upper motor neuron abnormalities, epilepsy and myoclonus.⁴

Cognitive and Psychiatric Abnormalities

Cognitive and psychiatric abnormalities are common among HD patients. Symptoms include dementia, depression, paranoia, schizophrenia and personality disorders. There also tends

to be a high rate of suicide or attempted suicide in this population.^{10,11} The diversity and apparently non-specific mental problems that may arise facilitate misdiagnosis of early stage HD, prior to the onset of motor abnormalities. Although several reports indicate that psychiatric symptoms occur prior to the onset of chorea or other motor abnormalities, there have also been reports of their occurrence after the onset of motor symptoms.⁴ The personality changes that occur in HD may be subtle in regards to linking them to neurological disease and may consist of increased degrees of antisocial (psychopathic) behavior, irritability, or aggression. Therefore, the diversity of psychiatric problems produced by HD can make it difficult to assess whether the mental symptoms began after the onset of motor difficulties or if they were present initially but went undetected.

A connection between HD and schizophrenia has been hypothesized for many years. Indeed, several reports have described the misdiagnosis of schizophrenia in patients that were later found to have HD.^{1,12,13} Three studies using standardized criteria for diagnosing schizophrenia reported the co-occurrence of HD and schizophrenia in 3/88 (3%),¹ 9/86 (10%)¹⁴ and 8/64 (12%)¹⁵ patients. The etiology of schizophrenia in HD patients remains unclear. There are conflicting opinions as to whether this condition is a direct result of the HD gene mutation or if patients with HD simply have an increased susceptibility to mental disorders.

Relationship Between HD Pathology and Symptomatology

Two forms of dyskinesia, chorea and bradykinesia/rigidity, follow in succession as HD progresses from early to late stages.^{16,17} The manifestation of chorea is thought to stem from specific alterations in the function of the basal ganglia. The caudate-putamen (striatum) receives massive input from cortical and subcortical regions and processes information primarily through efferent projections to the external segment of the globus pallidus (GPe), the internal segment of the globus pallidus (GPi), the substantia nigra pars reticulata (SNR) and the substantia nigra pars compacta (Figure 1).^{18,19} As striatopallidal neurons are particularly vulnerable to the effects of HD, it is believed that the chorea produced in early stages of HD results from a preferential loss of this circuit and a resultant disinhibition of the external (lateral) globus pallidus.²⁰⁻²³ The initial loss of the striatopallidal circuit disinhibits pallido-subthalamic neurons, ultimately reducing the nigral outflow and increasing thalamocortical and tectal stimulation. As the disease progresses, both indirect (striatopallidal) and direct (striatonigral) circuits are lost, producing Parkinsonian-like bradykinesia and rigidity (Figure 1). The notion that chorea results from reduced striatopallidal neurotransmission has been supported by numerous studies. In particular, Crossman and colleagues have demonstrated that infusing γ -aminobutyric acid (GABA) antagonists into the GPe, thus mimicking a reduction in striatopallidal transmission, produces contralateral chor-

eiform activity in primates.²⁰ Also, Young's group reported that, while rigid/akinetic HD patients had a significant loss of striatal neurons projecting to the GPe, GPi and the SNR, choreic patients had relative preservation of neurons projecting to the GPi.²¹ Furthermore, Storey and Beal reported greater losses of GABA in the GPe compared to the GPi in choreic HD, consistent with previous reports.²² Studies in our laboratory have shown that suppressing stimulant-induced striatal activity in rats produces sufficient stimulation of the ipsilateral GPe to induce massive changes in gene expression.²⁴ Ablation of GPe activity in this model significantly reduced the motor influence of the ipsilateral hemisphere, supporting the notion that GPe activation can markedly influence the motor responses in these animals.²⁵

Molecular Biology of HD

In 1993, the genetic mutation that produces HD was identified. A novel gene, termed Interesting Transcript 15 (IT15) was found to contain an abnormally expanded trinucleotide (CAG) repeat in patients with HD.²⁶ This polymorphic region lies within exon 1 of the IT15 gene and encodes a polyglutamine tract at the amino-terminal of the protein product. This protein, the function of which remains unknown, has been called huntingtin and is ubiquitously expressed throughout most brain regions as well as in peripheral tissues.²⁷⁻²⁹ Normally, the IT15 gene contains a stretch of 6-37 CAG repeats, whereas in patients with HD it has been found to contain >37 repeats. Individuals who develop HD symptoms in mid-life generally have between 37-45 CAG repeats, whereas in the juvenile form

of HD, patients tend to have greatly expanded repeat stretches, usually >50 CAG copies. In addition to HD, expansion of CAG trinucleotide repeats in genetic coding regions has been identified as a pathogenic mutation for several other neurodegenerative diseases, including spino-bulbar muscular atrophy (SBMA), spinocerebellar ataxia type 1 (SCA1), dentatorubral-pallidoluysian atrophy (DRPLA) and Machado-Joseph disease (SCA3).³⁰⁻³³ It is thought that the expansion of the polyglutamine tract on the respective protein products confers abnormal binding properties and causes novel or altered protein-protein interactions that ultimately produce toxicity and cell death.

The caudate-putamen is the most severely affected brain region in HD.¹ The regional selectivity of HD pathogenesis suggests that toxic interactions occur in the caudate-putamen which involve the mutant form of huntingtin and other regionally-specific proteins. A growing number of candidate proteins have been identified as possible interactive species, based on their increased binding efficacy to the huntingtin protein with an expanded polyglutamine tract. These include huntingtin-associated protein (HAP-1),³⁴ huntingtin-interacting protein (HIP-1),³⁵ the human ubiquitin conjugating enzyme, hE2-25K (HIP-2),³⁶ glyceraldehyde-3-phosphate dehydrogenase (GAPDH),³⁷ SH3-containing Grb2-like-3 (SH3GL3),³⁸ and several WW domain proteins (i.e. FBP-11).³⁹ Evidence also suggests that abnormal huntingtin may interact with well-characterized substrates such as calmodulin and the epidermal growth factor receptor.^{40,41}

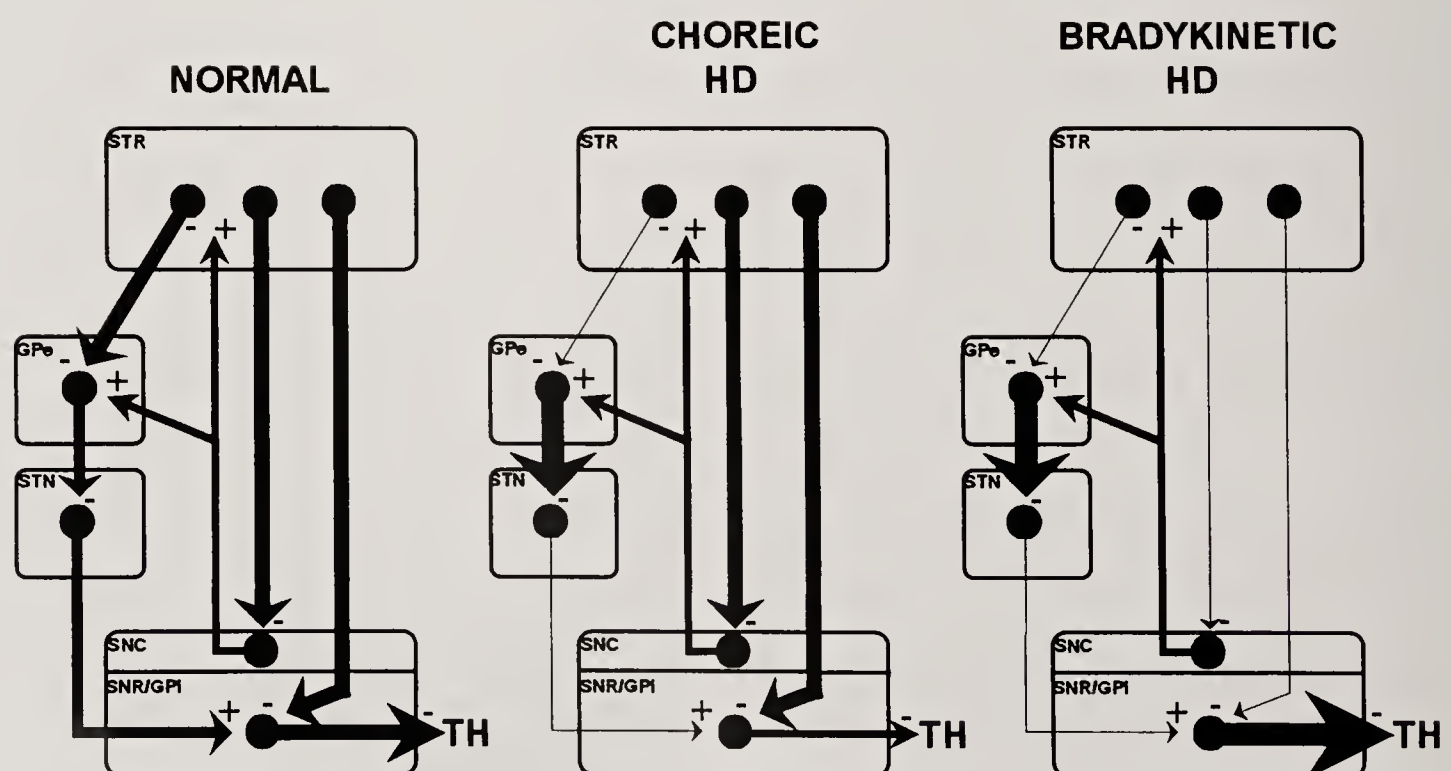


Figure 1. Simplified scheme of basal ganglia circuitry under normal conditions and in choreic and bradykinetic stages of HD. Arrow thickness represents the relative efferent activity from specific brain regions. The symbols at each arrowhead indicate whether that particular circuit is excitatory (+) or inhibitory (-). In choreic HD, striatopallidal neurons are lost, resulting in a disinhibition of the GPe and a subsequent reduction in excitation of the SNR/GPi by the STN. The reduction in SNR/GPi inhibition of thalamic regions increases thalamocortical stimulation of motor-associated regions of the cortex. During bradykinetic stages of HD, both striatopallidal and striatonigral neurons are lost. The resultant effect is a reduction of SNR/GPi inhibition and an increased inhibitory tone to the thalamus. This reduces thalamic stimulation of cortical regions and produces reduced motor output (bradykinesia). STR, striatum; GPe, globus pallidus (external segment); STN, subthalamic nucleus; SNC, substantia nigra pars compacta; SNR, substantia nigra pars reticulata; GPi, globus pallidus (internal segment); TH, thalamus.

Two principle foci remain at the forefront of current biomedical research into HD: 1. to determine the role of the huntingtin protein in the developing and adult central nervous system and 2. to determine the mechanisms that are invoked by expansion of the polyglutamine tract on huntingtin which lead to the neuropathology of HD. To date, several models have been used to study various aspects of HD, including quinolinic acid lesioning of the striatum (in rats),⁴² antisense-induced suppression of striatal stimulation (in rats)⁴³ and administration of 3-nitropropionic acid (an inhibitor of succinate dehydrogenase) to impair mitochondrial energy production (in rats and primates).⁴⁴ Additionally, genetic manipulations such as elongation of the CAG repeat region on the endogenous IT15 homolog (or other genes involved in similar CAG repeat disorders) or transfection of the human IT15 CAG expansion region have proven to be useful techniques in cultured cell lines, *Drosophila* models and in mice. Specifically, transgenic mice have been generated that have an insertion of exon 1 of the human IT15 gene into the host genome.⁴⁵ The inserted genomic fragments contained marked elongations of the CAG repeat region. These animals possess many characteristics of human HD, including a progressive neurological phenotype and the appearance of neuronal intranuclear inclusions (NIIs), aggregates of huntingtin-containing 'protein balls' in the nuclei of cerebral neurons. These NIIs have been previously found in brain tissue from HD patients.⁴⁶ Also, when compared to wild-type mice, analysis of the mRNA populations that are expressed in the striatum (the region most severely affected in HD) of these mutant mice has revealed significant alterations in gene expression. Some of these genetic alterations can be directly observed in the brains of HD patients (E. Denovan-Wright and H.A. Robertson, personal communication). Thus, this animal model is proving to be a powerful tool with which to identify specific genetic changes that are produced by the expression of an elongated polyglutamine tract on the amino-terminal of huntingtin.

The discovery of NIIs in both human HD and mouse HD brains has initiated a surge of experimental activity focused on determining the pathological significance of these aggregates. The mechanism by which nuclear aggregates are formed remains unclear. One possibility is that the elongated polyglutamine regions on the huntingtin protein increase hydrogen-bonding and form 'polar zippers' that enable these molecules to polymerize into a β -sheet or barrel conformation.⁶² Alternatively, evidence suggests that the expanded polyglutamine regions become preferred substrates for cellular enzymes called transglutaminases, which catalyze covalent (glutamyl-lysine) cross-linking reactions between polyglutamines and other polyamines, contributing to the formation of NIIs.^{48,63,64} This is supported by the finding that transglutaminase inhibitors can reduce aggregate formation in cultured cells that express expanded CAG repeat regions on the DRPLA gene.⁴⁸ Consistent with the positive correlation between CAG-repeat length and severity of disease, the rate of transglutaminase-

mediated polymerization of huntingtin has been shown to increase with the length of the polyglutamine region.⁶³

Studies have shown that, in HD, NIIs contain truncated, polyglutamine-containing huntingtin fragments, but little or no full-length huntingtin protein.⁶⁵ It has also been shown that truncated forms of the mutant proteins responsible for SCA3 (ataxin-3), DRPLA (atrophin-1) and SBMA (androgen receptor) assemble into nuclear aggregates.⁶⁶⁻⁶⁹ The insertion of a 146-unit CAG repeat into the mouse hypoxanthine phosphoribosyltransferase gene (*Hprt*), a so-called 'house-keeping' gene that has no association with any neurological disorders, produced a protein with an expanded polyglutamine region.⁴⁷ Interestingly, these animals also displayed a progressive neurological phenotype and, upon post-mortem examination, were found to contain NIIs. Thus, the process of NII formation appears to be independent of the gene containing the expanded CAG region. It was hypothesized that proteins with elongated polyglutamine regions undergo proteolytic cleavage in the cell to release truncated polyglutamine-containing peptides that form toxic nuclear aggregates. This hypothesis was supported by the discovery that the mutant huntingtin protein is a substrate for caspase-3, a cysteine protease that is involved in apoptotic cell death.⁷⁰ More recently, it has been shown that atrophin-1, ataxin-3 and the androgen receptor proteins are also subject to caspase-mediated proteolysis that produces small, polyglutamine-containing fragments.⁷¹ It appeared, therefore, that the elongation of the polyglutamine tract on intracellular proteins, elicits non-specific metabolic processes, including proteolysis and nuclear aggregate formation, that lead to the unique pathologies of the respective diseases. However, the link between the genetic mutation and the regional specificity of a particular disease (i.e., HD) remains unclear.

While there exists vast circumstantial evidence to implicate NIIs in the development of HD and other CAG-repeat diseases, the role of these aggregates in disease pathogenesis has recently been questioned. For example, Greenberg's group has shown that, while apoptosis was induced by the expression of mutant huntingtin in striatal cells, the incidence of cell death was not correlated to the formation of NIIs.⁴⁹ More recently, DiFiglia and colleagues have used caspase inhibitors to demonstrate the dissociation between the presence of NIIs and cell survival.⁷² Thus, the formation of NIIs may be a non-specific, benign manifestation of polyglutamine expansion. Alternatively, it has been suggested that these aggregates may actually reflect an attempt to protect the cell against imminent death.⁴⁹

Hypothesized Role of Huntingtin

Huntingtin is a large (350 kDa) cytoplasmic protein with unknown function and no known homology to other recognized proteins. The IT15 gene is expressed in both neural and non-neural tissue and is particularly high in the brain, lungs, ovaries and testes.²⁸ The widespread expression of huntingtin suggests that its cellular function is not a neuron-specific

process, but rather is common to both somatic and nervous tissue. Studies using gene knockout technology have shown that mice that have a homozygous deletion of the huntingtin gene die in utero. Animals with a heterozygous deletion, however, develop normally and are relatively indistinguishable from wild-type controls.⁵⁰⁻⁵² The survival of HD patients with homozygous mutations and the similarities of disease progression between heterozygous and homozygous HD individuals support the idea that, in HD, the normal function of huntingtin is preserved and the pathology results from a toxic 'gain-of-function'. Consistent with this notion, MacDonald's group has shown that mice that express reduced levels of mutant huntingtin have severe impairment of neurogenesis and die during development. However, when the level of mutant huntingtin is comparable to wild-type expression, the mice develop normally and are relatively indistinguishable from littermate controls.⁵³

Another study investigated the possible association of huntingtin with various signaling molecules involved in the epidermal growth factor receptor (EGFR) signaling cascade.⁴⁰ The presence of multiple proline-rich motifs in the huntingtin sequence led this group to investigate the possibility that huntingtin would associate with signaling modules through binding to src homology 3 (SH3) domains. The SH3 domain is a highly conserved sequence of amino acids present on intracellular proteins that are involved in the transduction of signals for cell polarization, motility, enzymatic activation and transcriptional regulation. Experiments demonstrated that huntingtin associates with the EGFR signaling complex through binding of SH3 domains on growth factor receptor-binding protein (Grb2) and Ras-GTPase-activating protein (RasGAP). Interestingly, huntingtin immunoprecipitates were found to contain Grb2, but not the Ras guanine nucleotide releasing factor, Sos. In contrast, Grb2 immunoprecipitates were found to contain Sos. As Sos is the normal associative molecule which complexes with the SH3 domains on Grb2, the authors suggested that huntingtin may be a competitive inhibitor of Sos-Grb2 binding and transduction of Ras-dependent signaling.

Consistent with the association between huntingtin and SH3 domains of signaling proteins, Wanker's group has reported interactions between huntingtin and the novel SH3-containing protein, SH3GL3, which is preferentially expressed in brain and testis.³⁸ While the function of this protein is unknown, there is 50-60% homology between the carboxy-terminals of SH3GL3 and Grb2, suggesting that there may be some similarity in function. Also, it has recently been shown that huntingtin has a polyglutamine-length -dependent association with a family of WW domain proteins, including HYPA, which has been implicated in spliceosome function.³⁹ The WW domain is involved in mediating protein-protein interactions and is found in various structural, regulatory, and signaling molecules in yeast, nematode, and mammals.

It has also been shown that the expression of huntingtin is dramatically elevated in astrocytes of the arcuate nucleus (AN) in lactating animals.⁵⁴ During this period, animals undergo significant physiological and anatomical restructuring in the AN, which permits lactogenic hormones to be produced. Most importantly, there is a great deal of evidence to suggest that the alterations in the AN are mediated by astrocytic regulation of neuronal activity.⁵⁵⁻⁵⁹ It appears that huntingtin may be an important component of the cellular mechanism that mediates hormone-induced transcriptional and morphological changes in the neuroendocrine brain.

The precise role of huntingtin in normal cellular function remains obscure. However, when taken together, the existing data suggests that huntingtin is involved in cytoskeletal restructuring which accommodates process growth, intercellular contacts or vesicle processing. This is further supported by reports of the colocalization of huntingtin with clathrin in endosomal preparations and with vesicle membrane proteins in isolated synaptosomes.^{60,61} Another possibility is that huntingtin is a component of a signaling cascade, likely involving SH3 or WW domain-mediated protein interactions. For example, the role of huntingtin as a regulator of receptor tyrosine kinase activity (i.e. EGFR signaling) would account for the widespread expression of this protein, as well as many of the findings reported in the literature. Of course, these two proposed functions of huntingtin may not be entirely distinct. For example, it is possible that huntingtin may mediate trophic effects (i.e. through EGFR regulation) that produce cytoskeletal restructuring in plastic neural circuits. In such a paradigm, the distinction between signaling and cytoskeletal roles may be difficult to assess. Clearly, more work needs to be done before the physiological role of huntingtin is fully understood.

Summary

Huntington's Disease represents one of a growing number of progressive neurodegenerative disorders that is caused by a CAG repeat expansion in a gene of unknown significance. Both the clinical profile and the neuropathology of HD are well recognized. However, the connection between these two entities remains unclear. Determination of the relationship between CAG repeat expansion, regional neuropathology and the observed neurological phenotype of HD offers the potential for the development of therapeutic strategies for a host of diseases with similar etiologies.

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Tumour Suppressor Gene Therapy

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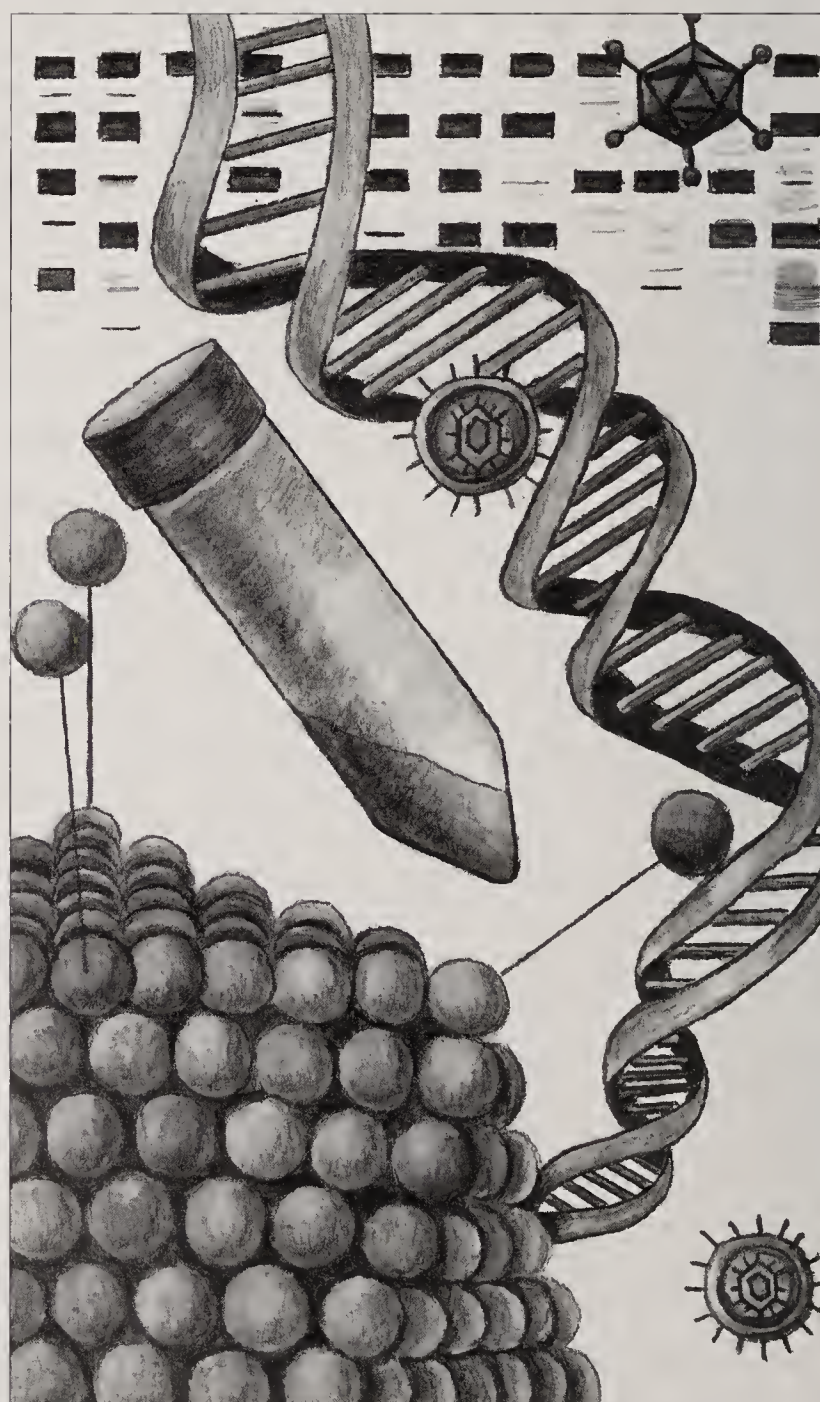
Abstract

Through the synthesis of multiple disciplines including pathology, biochemistry, virology, and more recently molecular biology, a field has emerged with the potential to treat disease by changing the genetic makeup of a cell. Gene therapy consists of two basic components: choosing an appropriate delivery vehicle, or vector, and the appropriate therapeutic gene. Retrovirus, adenovirus, and liposomes are currently the most widely used vectors, each having its own advantages and disadvantages. Since the discovery that cells contain genes that act as natural anti-tumorigenic agents, tumour suppressor genes have become attractive candidates for use in anti-cancer gene therapy. This review will discuss the aforementioned vectors, some tumour suppressor genes, some of the results of their use in gene therapy, as well as some future directions.

Gene Therapy

Gene therapy is a rapidly emerging field that has come into its own only in the past 15 years. It includes, among other things, gene-replacement therapy, immunotherapy, and insertion of a gene whose protein can convert a pro-drug into a cytotoxic molecule. The latter two do not include insertion of genes that are directly therapeutic. It has therefore been suggested that these cases be considered gene therapeutics, rather than gene-replacement therapy.^{1,2} While a focus of gene therapy research in the 1980's was the correction of inheritable diseases by transformation of hemopoietic stem cells,³ the field has gradually shifted towards examination of its usefulness as an anticancer

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therapeutic.⁴ With this new technology has arisen an international debate concerning gene therapy's ethical implications, beginning even before the technology was available. "No other form of therapy known to medical history has ever been subjected to such strict control in its development and clinical trials as human somatic gene therapy."⁵ Each aspect of gene therapy has its own considerations. While human somatic gene transfer is generally regarded as an acceptable extension of medical technology, germ-line gene transfer is somewhat more controversial, even to the point of human embryo work being banned in France and Germany to prevent germ-line experiments.⁵ As well, the U.S. company AntiCancer Inc has applied to the FDA for rights to use gene therapy for the restoration of hair loss following chemotherapy. A conference organized by the NIH in 1997 concluded extensive gene therapy use for cosmetic purposes such as this has its own potential problems.⁶

Clinical gene therapy/therapeutics trials began within the past 10 years. Currently, the majority of these are anticancer trials.² In Canada, the number of clinical trials has grown from 1 in 1994 to 6 in 1998. Worldwide, approximately 3,000 patients in 14 countries on 270 protocols are involved in gene therapy/therapeutics clinical trials. Over 50 companies have become involved, making it a \$3 billion a year industry.⁷ Typically, small biotechnology companies started by academics around novel or proprietary technology have been leading the advance of gene therapeutics development. The oldest of these companies were founded in the late 1980's. More recently, large pharmaceutical and biotechnology companies such as Boehringer Mannheim, Rhone-Poulenc-Rorac (RPR), Pfizer, and Chiron have taken an interest in this field by acquiring or investing in these smaller firms. With RPR GenCell, RPR has invested \$100 million a year bringing together firms and public research institutions from France and the U.S. covering a broad range of gene therapy-related technologies.⁸ Princess Margaret Hospital in Toronto is also currently engaged in an RPR gene therapy head and neck cancer clinical trial.

The principle vectors being tested in clinical trials in Canada are adenovirus, followed by retrovirus and liposomes.⁷ Worldwide, the principle strategies are immunotherapy, prodrug gene therapeutics, and tumour suppressor gene therapy, with retrovirus and adenovirus being the most frequently used viral vectors.² This article will review the most commonly used vectors currently adopted for gene transfer, as well as defining several tumour suppressor genes and the results of their use in somatic cell cancer gene therapy.

Gene Delivery

A fundamental obstacle to the full realization of gene therapy's potential is the development of an efficient gene delivery vehicle. Ideally, one would like to deliver a vector carrying a therapeutic gene systemically, either intravenously or orally, and have the vector specifically target tumour cells. Unfortunately, many of the current vectors are trapped in the liver, and in the case of viral vectors, may induce an immune response against further challenge with the same vector. This has forced much of the solid

tumour gene therapy field towards improving local control in the short term, with mixed results in terms of optimal vector distribution within the tumour. For the long term, there has been an increasing effort to target gene therapy vectors to tumour cells. The results of the bulk of tumour targeting research will not be discussed. Instead, this section will include a general overview of some common gene therapy vectors, including their advantages and disadvantages, and some future directions.

A. Retrovirus

Retroviruses, such as the Moloney murine leukemia virus,⁹ contain an RNA genome packaged into a capsid protein core, surrounded by viral glycoproteins in a lipid bilayer originating from the previously infected cell.¹⁰ Retroviruses contain the *gag*, *pol*, and *env* genes, which are required for viral replication. Replication-deficient retroviruses have been developed by mutating these genes and inserting complementary copies in packaging cell lines.¹¹ Therefore, the disabled recombinant viral vector containing an inserted therapeutic gene can only replicate in the packaging cell line, but the resulting viruses produced by the packaging cells are still capable of infecting other cells. This is an attempt to control the therapy by limiting its effects to an initial target population and its vicinity.

Many retroviruses integrate randomly into the host cell's genome, which creates the potential problem of insertional mutagenesis. However, insertion also results in permanent expression of the therapeutic gene, which is of great benefit in the correction of genetic defects such as cystic fibrosis. Retroviral vectors also possess the advantage of limited immunogenicity due to the removal of viral genes.

A major problem with the use of some retroviruses in anti-cancer gene therapy is that they are only capable of infecting dividing cells.¹² This could be an obstacle in the treatment of entire tumours, since tumours consist of cells at various stages of the cell cycle.¹⁴ If one were interested in targeting brain tumours such as glioblastoma multiforme,¹⁴ however, this might be helpful. In this instance, the normal non-dividing surrounding brain tissue might be spared, relative to that of the tumour and its growing vasculature, from the effects of the retroviral gene therapy.

Recent attempts to overcome the obstacle of infecting only dividing cells have utilized a disabled human immunodeficiency virus capable of infecting non-dividing cells.¹⁵ A principal question still to be addressed for this lentiviral vector, however, is its safety for human use.¹⁶

B. Adenovirus

There are over 100 serotypes of adenovirus, with over 40 of these tropic for humans. The most frequently used human serotype in gene therapy is type 5. Wild-type adenovirus type 5 normally infects the epithelium of the respiratory tract, making it a good candidate for use on epithelial malignancies. Due

in part to the pioneering work of Frank Graham at McMaster University, adenovirus has gained in popularity over the years as a vector for gene therapy. It appears relatively safe. Wild-type adenovirus has been used as a vaccine for many years with no detectable side-effects.¹⁷ The viral genome has been well-characterized, and deletion of early region 1 (E1) renders the virus infectious but replication-defective. Therefore, it can only propagate in a packaging cell line containing a complimentary E1 region. Further deletion of the non-essential early region 3 (E3) allows up to 7.5 kb of exogenous DNA to be inserted,¹⁸ which is similar to retroviruses. A therapeutic gene under the regulation of a strong promoter can then be inserted in place of the E1 or E3 region. Adenoviruses are relatively easily manipulated, exhibit high infectivity in a broad host range, and infect non-dividing as well as dividing cells.¹⁹

Adenoviruses can be routinely grown to a titre of 10^{11} pfu/mL (pfu = plaque forming units, a measure of infectious dose) as compared to retroviruses at 10^7 pfu/mL.^{2,16} The virus and the inserted therapeutic gene are episomal, as adenoviruses do not need to incorporate into the host cell's genome like retroviruses. This reduces the risk of insertional mutagenesis,¹⁹ but limits the therapy to transient expression of the therapeutic gene in a population of dividing cells. This may not be an obstacle in tumour suppressor gene therapy, however, where the ablative effects are immediate.

An important consideration in using traditional E1- and E3-deleted adenoviruses is their tendency to elicit an immune response, which further shortens the duration of therapeutic gene expression *in vivo*.²⁰ A low level of viral protein expression following infection makes them more immunogenic than retroviral vectors. One method used to reduce immunogenicity, as well as to increase the vector's DNA insert size capacity, involves the use of "gutless vectors." These vectors have all their viral coding sequences removed, thus allowing a DNA insert of roughly 37 kb to be packaged in the vector. This has also prolonged transgene expression by reducing the immune response to viral proteins in immune-competent animals.^{21,22}

C. Liposomes

Lipid vesicles or liposomes are also used to deliver DNA and drugs to tumour cells. The concept for using liposomes as vehicles in human gene therapy originated from earlier attempts to improve DNA transfection efficiency *in vitro*.²³ Negatively charged plasmid DNA will associate with positively charged liposomes (cationic liposomes), as will cell membranes. The DNA can then pass through the cell's external lipid bilayer and is expressed in the nucleus, as in traditional plasmid transfections. Liposome-mediated gene transfer has been found to be safe in animals²⁴ and in humans,^{25,26} and liposomes are able to insert DNA into a wide variety of cell types.²⁷ Cationic liposomes carrying DNA overcome some of the complications found in some viral vectors. Liposomes are amenable to repeated use without stimulating a neutralizing immune response that affects

re-expression of the therapeutic gene.²⁸ They are also capable of carrying large amounts of DNA.²⁹

Liposome use in gene therapy faces the major obstacle of low transfection efficiencies obtained even *in vitro* as compared to viral vectors.³⁰ Also, upon intravenous injection, liposomes are trapped in the liver and taken up by macrophages.³¹ Many investigators have developed methods to improve transfection efficiency as well as increase transfection at the tumour site *in vivo*. This has involved changing the plasmid DNA itself,²⁸ the structure of the lipid complex,^{32,31} or adding ligands to take advantage of receptor-mediated endocytosis.^{33,34} One intriguing finding is that the use of smaller, more stable, uncharged liposomes have improved delivery to tumours upon intravenous injection. It is thought that by being better able to escape immune detection, and by remaining in the circulation longer, they preferentially extravasate in areas with leaky vasculature, such as that found in solid tumours.³¹

Tumour Suppressor Genes

Tumorigenesis is currently recognized as a multifactorial process³⁵ that may include the conversion of proto-oncogenes to oncogenes;^{36,37} the inhibition of tumour suppressor genes;³⁸ or a combination of these events.³⁹ It can be due to genetic mutations, rearrangements, or deletions. Tumour suppressors include such genes as *RB*, *p16*, and *p53*. While proto-oncogenes undergo activating mutations or rearrangements to become overexpressed or constitutively activated oncogenes, tumour suppressor genes typically undergo inactivating mutations or deletions during tumorigenesis. Tumour suppressor gene therapy is designed to restore or enhance a tumour cell's inherent tumour suppressor capabilities, leading to growth inhibition and/or programmed cell death, or apoptosis. Apoptosis is a controlled process characterized morphologically by cellular membrane blebbing, cell shrinkage, and chromatin condensation. Biochemically, it can be detected by DNA fragmentation visualized with agarose gel electrophoresis.⁴⁰ Apoptosis provides a mechanism whereby cells may self-terminate upon sensing irreparable DNA damage.

A. Retinoblastoma Gene (*RB*)

The *RB* gene was isolated in the 1980's,^{41,42} making it the first gene found that causes human cancer. Loss of *RB* function causes hereditary retinoblastoma, a tumour that develops in children's eyes in the majority of those who carry a germline mutation. Studying this cancer led Knudson⁴³ to the groundbreaking conclusion that retinoblastoma development required two mutations in embryonic precursor cells in the eye, thus laying the groundwork for our current understanding of tumorigenesis as a multi-hit process. For a good discussion of retinoblastoma genetics, see reference 44. *RB* has since been found to play a role in cell cycle regulation. While hypophosphorylated, the *RB* gene protein product, pRB, can bind and inactivate the E2F transcription factor.⁴⁵ It also binds to a consensus sequence within a number of promoters, inhibiting tran-

scription of genes involved in advancing cells through G1 to the S phase of the cell cycle (reviewed in 46). pRB is negatively regulated by cyclin and cyclin-dependent kinase (CDK) complexes, which phosphorylate pRB and cause it to release E2F47 (see Figure 1), allowing cells to progress through the cell cycle.

Loss of functional pRB has been associated with a variety of malignancies in addition to retinoblastoma, both as an early event in tumorigenesis and at later stages during tumour progression.⁴⁸ Gene therapy delivering wild-type RB has been used in attempts to restore pRB cell cycle control in tumour cells *in vitro* and *in vivo*.^{49,50} One group has used a truncated pRB that tends to remain in an unphosphorylated form to enhance RB gene therapy in bladder xenograft tumours in mice.⁵¹ RB gene therapy may also benefit from the potential role of pRB in increasing the immunogenicity of tumour cells⁵² and suppressing tumour cell invasiveness.⁵³

An intriguing paper published in late 1997 attempted to take advantage of RB loss in malignant gliomas by using an adenoviral vector with an E2F promoter.⁵⁴ The reasoning was that since pRB normally suppresses E2F-responsive promoters, gliomas that lack pRB may have more activated E2F-responsive promoters than normal surrounding tissue. Therefore, gene therapy utilizing an E2F promoter may preferentially target the tumour over normal tissue. This was in fact what was found. The E2F promoter appeared to very selectively express a reporter gene in established rat glioma cell line tumours in rat brains, while a virus with a non-discriminating promoter was active throughout the brain. Introduction of an E2F promoter-regulated herpes simplex virus thymidine kinase gene in combination with ganciclovir (GCV), which is converted into a cytotoxic agent by the kinase, did not appear to cause toxicity in normal brain. However, this regimen was very toxic when a non-discriminating viral promoter was used. The pictures in the paper are striking, but the relevance in humans remains to be determined.

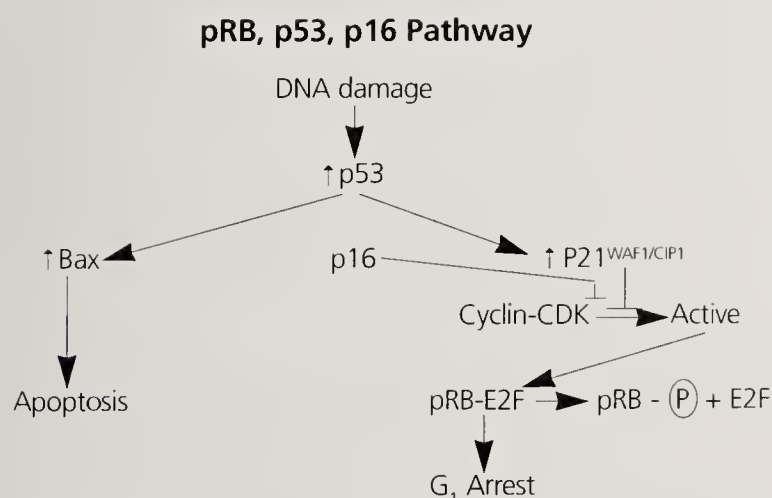


Figure 1. Abridged pRB, p53, p16 pathway. Following DNA damage, p53 may accumulate and transactivate p21, leading to inhibition of cyclin-CDK complexes' ability to phosphorylate pRB. Consequently, this may result in G1 arrest due to pRB inhibition of E2F transcriptional activity. p53 is also capable of driving the cell toward apoptosis through stimulating accumulation of Bax. p16 is capable of inhibiting cyclin-CDK activity by sequestering CDKs and inhibiting cyclin binding, thus also potentially leading to G1 arrest.

B. p16

The *p16* cDNA was isolated in 1993 and was found to inhibit cyclin-CDK activity, specifically the activity of the cyclin D-CDK4 complex.⁵⁵ This placed *p16* (also called MTS-1 for major tumour suppressor 1, INK4a for inhibitor of cyclin-dependent kinase 4a, and CDKN2A for cyclin-dependent kinase inhibitor 2A)⁵⁶ in the RB pathway. By binding to CDK4 and inhibiting cyclin D, *p16* prevents phosphorylation of pRB, leading to cell cycle arrest in G1⁵⁶ (Figure 1). *p16* has been found to be mutated or deleted in a wide variety of tumour types,^{57,58,59} suggesting it is potentially a critical player in tumorigenesis. In an effort to restore *p16* function to tumours, several groups have examined *p16* gene therapy in multiple tumour types. A growth inhibitory effect was found with this treatment both *in vitro* and *in vivo*, and some tumour regression was also reported.^{60,61} The efficacy of *p16* may be limited to cancer cells with a certain *p16* and *RB* profile. It appears *p16* gene therapy may be more cytotoxic to tumour cells that are mutant or null for *p16* but retain normal *RB*, versus tumour cells that have lost *RB* but have retained normal *p16*, a finding that further links *p16* and *RB*.⁶²

A concern in using *p16* gene therapy in combination with chemotherapy is its apparent potential to confer chemoresistance to cancer cells.⁶³ Another potential complication is that *p16* can actually lead to reduced *RB* mRNA and pRB expression.⁶⁴ The mechanism for this effect is unclear. It may be due partly to *RB* autorepression,⁶⁵ but this does not explain the entire effect.⁶⁴ It has been suggested that this decline in pRB levels may compromise *p16* gene therapy, perhaps requiring co-introduction of *RB* along with *p16*.⁶⁴ A decrease in total pRB following overexpression of *p16* was also found in an earlier paper combining *p16* and *p53* gene therapy in hepatocellular carcinoma.⁶⁶ However, this decrease resulted in their model in prolonged cell cycle arrest and some apoptosis, more often in cells harboring wild-type than mutant *p53* (Figure 1). The apoptosis observed following *p16* delivery was enhanced by concomitant overexpression of *p53*. However, *p53* overexpression did not appear to cause tumour cells with normal pRB to undergo apoptosis in the absence of overexpressed *p16*. This suggests that using *p16* to block the normal pRB pathway, along with the subsequent decrease in pRB expression, enhances the ability of overexpressed *p53* to initiate apoptosis. Therefore, one might want decreased pRB levels in order to cause tumour cell death via *p53*-mediated apoptosis. More work needs to be done in this area to determine the mechanism and judge if the events described are universal or limited to certain tumour types or cell lines.

C. p53

Mutations in the *p53* gene are among the most common genetic defects identified in human malignancy.⁶⁷ When functioning normally, *p53* acts as a tumour suppressor gene. The wild-type protein can initiate cell cycle arrest mediated through *p21* (WAF1/CIP1) in response to DNA damage⁶⁸ (Figure 1) and may also be directly involved in DNA repair.⁶⁹ *p53* appears to

be an important determinant for both proliferation and apoptosis. Bax, a pro-apoptotic protein⁷⁰ (Figure 1), may be a mediator of *p53*-dependent apoptosis.⁷¹ In fact, a loss in the normal ability of *p53* to induce Bax has been found to confer resistance in tumour cells.⁷² Wild-type *p53* protein accumulates following exposure to ionizing radiation,⁷³ and others have shown *p53* to be capable of regulating the cytotoxic effects of ionizing radiation and chemotherapeutic drugs on cells.⁷⁴ Mutant forms of *p53*, on the other hand, may inactivate wild-type *p53* by binding to it,⁷⁵ while different mutants appear to stimulate tumour growth,⁷⁶ thus revealing oncogenic potential for some *p53* mutations.

Over the past few years, there have been numerous papers examining the effects of exogenous *p53* gene transfer on a variety of cancer cell lines and "normal" cells *in vitro* and *in vivo*.^{77,78,79,80,81} As well, since *p53* may enhance the cytotoxicity of ionizing radiation and some chemotherapeutic drugs, the use of *p53* gene therapy in combination with these therapeutics has also been examined.^{82,83,84,85}

Even if there is poor distribution of therapeutic gene expression within a tumour, use of the *p53* gene may be able to partially overcome this problem by taking advantage of the "bystander effect." This is an effect whereby neighbouring non-transduced cells, "bystander" cells, die along with those that were successfully transduced, effectively increasing the treated tumour area. This effect has been found typically in gene therapy using the thymidine kinase gene in combination with ganciclovir.⁸⁶ Recently, however, a bystander effect has been observed with *p53* gene therapy.⁸⁷ *p53* has also been shown to downregulate vascular endothelial growth factor (VEGF), a stimulant of angiogenesis,⁸⁸ which may partially explain the mechanism behind a bystander effect with *p53* gene therapy.⁸⁹ Tumours need to recruit new blood vessels in order to grow past a certain size.⁹⁰ Without supportive vasculature, a tumour is limited in size to the maximum distance oxygen and nutrients can diffuse from the closest blood vessel. If *p53* gene therapy suppresses blood vessel growth surrounding the tumour, it would adversely affect non-transduced cells by limiting their blood supply.

The success of *p53* gene therapy *in vitro* and *in vivo* in animals has resulted in a push to clinical trials. The results of some phase I trials have already been published.^{91,92,93,94} In these trials, *p53* gene therapy was found to be generally well tolerated. The earliest study, injecting retroviral-*p53* gene therapy in non-small cell lung carcinoma, found 3 of 7 patients to complete treatment demonstrated tumour regression, with 2 of these 3 patients benefiting from complete regression at the treated site from 1-3 months post-treatment. The patients included in this trial eventually died of causes unrelated to the treated tumour site.⁹¹ In an adenovirus-*p53* phase I trial in head and neck squamous cell carcinoma, 2 out of 17 patients showed tumour regression of greater than 50% following treatment.⁹² The authors plan to undertake phase II clinical trials. Other cancers are also being included in *p53* gene therapy clinical trials.²

Conclusions

Regardless of the vector or therapeutic gene used, gene therapy remains today with the challenges of sub-optimal distribution and poor selectivity *in vivo*. Much of the anti-cancer gene therapy community is therefore currently approaching this potential therapeutic as an adjuvant to other therapies, including the more traditional surgery, radiation therapy, and chemotherapy regimens. There has been a tremendous amount of work surrounding improved targeting strategies with inducible promoters specifically turned on by these and other therapies;^{95,96,97} with tissue-specific promoters;⁹⁸ and even with selection of the therapeutic gene, like *p53*, for optimal synergy with radiation or chemotherapy.^{74,85}

Recently, there has been interest in using recombinant viruses alone as anti-cancer therapeutics. By exploiting some of the many mutations that frequently occur in cancer, several labs have constructed viruses that are designed to be capable of completing their life cycle (including the rupture of infected cells and release of new virus) only in tumour cells. These so-called "oncolytic viruses" now include several types of viruses. The most recent addition to this group is a modified reovirus from a laboratory at the University of Calgary.⁹⁹ The ONYX-015 adenovirus is the furthest along in clinical trials.^{100,101} It has been altered such that the authors claim it should only be able to complete its life cycle in *p53*-deficient or mutant cells, i.e. cancer cells. Even though the ONYX-015 appears to be promising in clinical trials,¹⁰² the mechanism of its action and selectivity has recently been disputed.¹⁰³ These new findings suggest that even though the virus may kill cancer cells, its tumour targeting ability may have little to do with tumours being *p53* deficient.

Much is known about viral genetics and tumour suppressor genes, but this apparent contradiction in the literature serves to highlight major limits in our current understanding. However, it is important to remember that despite all the media attention, gene therapy is a very young field. The more we know, the easier it will be to design vectors that target tumour cells and perhaps be specific enough to deliver systemically. Using the results of the human genome project, it might become feasible to devise gene therapy strategies tailor-made for the genetic profile of individual patients. As the search for the perfect vector and the perfect message progresses, gene therapy will come into its own as a powerful new therapeutic.

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Post-Streptococcal Reactive Arthritis in Children: A Review of the Literature

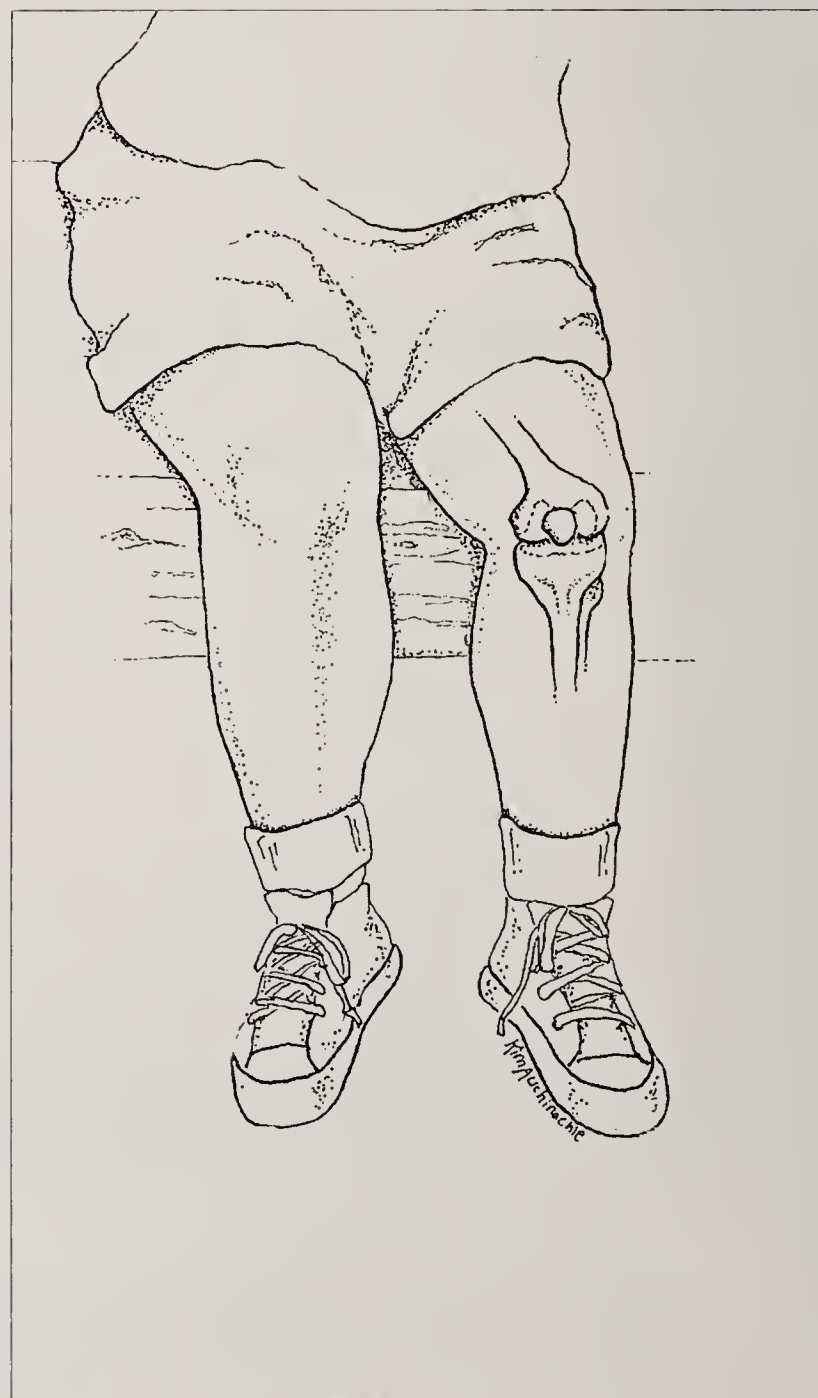
Lani Lieberman, BA (9T9), and Nina Birdi, MD, FRCP(C)*

Abstract

With the resurgence of acute rheumatic fever (ARF) and post-streptococcal reactive arthritis (PSRA) over the past decade,¹ it has become increasingly important to understand the definition, presentation and treatment options for these two diseases. Pediatric emergency physicians, general pediatricians as well as primary care physicians all play an integral role in the accurate diagnosis and management of these disease. This review article presents the definition and presentation of PSRA, compares its clinical features with that of ARF, discusses etiologic theories, provides an approach to diagnosis, and presents the controversial issues that remain regarding management.

Introduction

Scarlatinal arthritis or post-streptococcal reactive arthritis (PSRA) was first observed in 1959 by Crea and Mortimer,² who described eighteen patients (only two over the age of 16) with non-suppurative arthritis and a history of scarlet fever. Eighty-nine percent (16/18) of these patients did not have carditis or any other major manifestations of the Jones criteria for acute rheumatic fever (ARF) at the time of diagnosis (See Table 1). Upon re-examination one to twenty years later, 2 patients had subsequently developed acute rheumatic fever (ARF), 6 had evidence of rheumatic heart disease (RHD) and 8 others (including the two adults) had no further problems. Overall, 10 (56%)



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of the patients had a subsequent history to suggest a diagnosis of ARF. At this time, it was concluded that scarlatinal arthritis was probably a variant of ARF and that patients should be treated with prophylactic antibiotics against future streptococcal infections. There were no further reports of PSRA until the 1980s, when outbreaks of ARF were reported in a number of areas, including Salt Lake City Utah, Akron and Columbus Ohio, Pennsylvania, New York, Nashville Tennessee, Texas, West Virginia, and in military populations.^{1,14} The resurgence of ARF was believed to be due to alterations in the rheumatogenicity of Strep (i.e. different strains are being isolated in recent outbreaks that were previously not very frequently seen). This explanation is felt to be more likely than environmental factors (poverty, overcrowding) given that recent outbreaks are in middle class populations from rural or suburban areas.

Table 1*
Revised Modified Jones Criteria

Major Criteria

- carditis
- polyarthritis
- erythema marginatum
- subcutaneous nodules
- chorea

Minor Criteria

- Clinical Findings
 - 1. arthralgia
 - 2. fever
- Lab Findings
 - 3. elevated acute-phase reactants (ESR or CRP)
 - 4. prolonged PR interval
- Previous History
 - 5. previous rheumatic carditis

Supporting Evidence of Antecedent GABHS Infection

- positive throat cultures
- rising streptococcal antibody titer
- recent scarlet fever

**From the Special Writing Group of the American Heart Association: The diagnosis of rheumatic fever. JAMA; 2069-2073, © 1992, American Medical Association.*

Methodology

This literature review which focuses on presentation, investigations and management of PSRA is based on articles obtained from a Medline search between the years of 1990-1998 inclusive. The key words utilized in the strategy include post-streptococcal reactive arthritis, rheumatic heart disease, prophylactic treatment and group A streptococcus. Additional articles dating back to 1959 were cross referenced from the original articles obtained. The majority of the articles utilized included case reports and review articles on the topic of ARF and PSRA.

Table 2*
Revised Modified Jones Criteria

	ARF	PSRA
Epidemiology		
Age	5-15	3-15
Sex ratio (male: female)	1:1	1:1
Chorea	0-30%	0
Erythema marginatum	0-13%	0
Carditis	30-90%	rare cases reported
Nodules	0-8%	0
Arthritis		
Flitting	+++	-
Persistent	-	+++
Large joints	+++	+++
Small joints	±	+++
Salicylate response	+++	inconsistent
Erosive	-	-
Preceding streptococci infection	requirement for diagnosis	
Approximate interval between infection and disease in days	21	10
Association with B-cell alloantigen D8/17	+++	+++ ***

ARF = Acute rheumatic fever
PSRA = Post-streptococcal reactive arthritis
**Data from CJID, 6 (3): 133-135, 1995.
***Data from:
• Zemel LS, Hakonarson H, Diana DJ and JB Zabriskie. (1992). Post-streptococcal reactive arthritis: a clinical and immunogenic analysis (abstr). J Rheumatol. (suppl 33)19:120.
• Birdi N, Allen U, Hosking M, Zabriskie JB. (1995). B-cell alloantigen D8/17 testing in children with ARF and PSRA. Arthritis and Rheumatism. 39: 59.

Definition and Presentation

PSRA is a poorly understood clinical syndrome which lacks clear diagnostic criteria and treatment recommendations. The term PSRA refers to a reactive arthritis characterized by a pharyngeal streptococcal infection, a symptom free interval of approximately ten days followed by aseptic inflammation of one or more joints.³ The arthritis presentation may mimic acute septic arthritis with a sudden onset of fever, severe joint pain and refusal to weight bear. The pain is often out of proportion to the degree of physical findings.⁴ There is no specific pattern to the joint involvement; it may be monoarticular or polyarticular, migratory, additive or chronic. The arthritis tends to be less dramatic than that of ARF, is usually non-destructive and self-limited, but the symptoms can last for weeks or months. The response to aspirin (ASA) or non-steroidal anti-inflammatory medication (NSAIDs) may be slower than with ARF. There may not be clinical evidence of a preceding streptococcal infection and the throat culture may be negative.³ Table 2 lists the similarities and differences between PSRA and ARF.⁵

PSRA refers to patients with a Group A Beta hemolytic streptococcal (GABHS) infection who do not fulfill the modified

Jones criteria (See Table 1) for a diagnosis of ARF.⁶ In other words, PSRA refers to reactive arthritis without cardiac or central nervous system involvement occurring after a streptococcal infection.³ Nonetheless, there have been several reports of pediatric patients who have subsequently developed carditis.^{2,6-8}

Etiology

Reactive arthritis is defined as a sterile, culture negative, inflammatory polyarthritis occurring in association with an infection at a distant site.^{9,10} The arthritis can occur following an upper respiratory tract infection (GABHS pharyngitis), gastrointestinal infection (Salmonella, Shigella, Yersinia, Campylobacter) or genito-urinary (GU) infection (Chlamydia). The term reactive arthritis implies that no organism is recovered from the joint space, but that an infection has occurred elsewhere in the body, with presumed immunologic cross-reactivity between the infecting organism and synovial antigens. This results in synovial inflammation directed to a site distant from that of the initial infection.⁴ The exact etiology remains unclear. To date, there has been no association made between PSRA and HLA-B27 in pediatric patients.¹¹ This contrasts with other forms of “reactive arthritis” (such as Ankylosing Spondylitis, Reiter’s Syndrome, arthritis of IBD) where over 90% of patients test positive for HLA-B27.

Differential Diagnosis

Although clinical criteria help to differentiate PSRA from other illnesses, other diseases should be considered in the differential diagnosis before a final diagnosis is made. These include juvenile rheumatoid arthritis (JRA), spondyloarthropathies, viral arthritis, septic arthritis and reactive arthritis secondary to enteric (Yersinia, Campylobacter, Salmonella) or GU tract infections (Chlamydia). It is often difficult to differentiate these diseases from PSRA. Other reactive arthritides are also characterized by an acute onset with associated pain, while most children with systemic onset JRA have a spiking fever pattern and characteristic salmon pink evanescent rash. In addition, the most frequent cardiac finding in JRA is isolated pericarditis, a finding which should not occur in ARF or PSRA. Most children with other types of JRA present with an insidious onset of stiffness, swelling, limp and severe pain which is uncharacteristic of PSRA and ARF. These two diseases can also be confused with septic arthritis.⁴ When there is an acute onset of painful arthritis, Streptococcal antibodies should be done and titres repeated to confirm a recent Streptococcal infection, a sine qua non of a diagnosis of ARF or PSRA. When there is a short lived arthritis following a viral infection without evidence of preceding Streptococcal infection, then a viral or post viral etiology is presumed (“transient synovitis”).

Investigations

The following tests should be ordered when investigating for PSRA or ARF:

1. Complete blood count with a differential to help differentiate between inflammatory and infectious versus other causes.
2. Acute phase reactants such as ESR (erythrocyte sedimentation rate) and CRP (C reactive protein) which are inflammatory markers.
3. A throat culture for GABHS, although this may be negative at the time of presentation.
4. Blood cultures to rule out sepsis.
5. Chlamydial swabs (if patient is sexually active) to rule out chlamydia as a cause of reactive arthritis.
6. Stool cultures for bacterial pathogens (such as Salmonella, Shigella, Campylobacter, Yersinia) to rule out reactive arthritis associated with enteric infections. This test would be particularly important if any history of a diarrheal illness is present.
7. Synovial fluid cultures, cell count and differential if septic arthritis is clinically suspected, especially if there is fever and monoarthritis (not done routinely).
8. Serologic tests for GABHS infection [ASOT (antistreptolysin O titre), anti-DNAse B, antihyaluronidase A titre].
9. An electrocardiogram to look for a prolonged PR interval and an echocardiogram searching for a possible valvulitis, myocarditis or pericarditis. Any patient with cardiac involvement should be referred to a pediatric cardiologist for close cardiac follow-up.

Bloodwork usually indicates an increased white blood cell (WBC) count with elevated levels of ESR and CRP. The synovial fluid WBC count can be as high as $>100 \times 10^9/L$ (often in the “inflammatory range”, normal value $\approx 5.0-15 \times 10^9/L$) and the synovial and blood cultures are usually negative. When there is a clinical suspicion of PSRA or ARF, a definitive diagnosis requires documentation of a recent Streptococcal infection (recent diagnosis of scarlet fever, a positive throat culture or serologic evidence of GABHS). A positive throat culture helps to support the diagnosis but many factors often complicate this result. Many children are healthy, asymptomatic chronic GABHS carriers and a positive throat culture from these children does not necessarily imply a true infection. In addition, GABHS may not be in the throat when the non-suppurative complications (such as PSRA) appear due to effective anti-microbial therapy or spontaneous clearance.⁵ The most reliable way to prove a true infection is to demonstrate that an immune response to the organism has taken place with anti-streptococcal antibody testing. Unfortunately, serological evidence of a recent infection is not present immediately and it usually takes two to four weeks to see an increase. Performing serial serologic tests (e.g. ASOT, anti-DNAse B, antihyaluronidase A antibody) can improve the sensitivity of detecting recent Streptococcal infection.¹² When two antibody assays are used, 95% of patients with ARF will have an increased titer of at least one antibody.⁴ Paired ASO titers are more helpful than a single elevated titer, especially if the first titer is only mildly elevated.³ A repeat titer one to two weeks after presentation is strong evidence of a preceding infection, but only if there is a two-fold rise in antibody titres (one titre increase is within range of laboratory error).¹³

Treatment and Complications

Once the diagnosis of ARF or PSRA is made, antibacterial therapy should always be given to completely eradicate the organism if GABHS is recovered from the throat. The long-term risk of developing rheumatic heart disease (RHD) following PSRA has not yet been determined which complicates the decision regarding the optimal management options.³ In ARF, prophylactic antibiotics prevent the recurrence of ARF and the potential additional morbidity of recurrent episodes of carditis. Because overt or silent mitral valvular insufficiency may accompany PSRA and patients with PSRA experience recurrences, some researchers recommend that all individuals with PSRA be treated with long term penicillin antibiotic prophylaxis (as recommended for patients with ARF).^{2,6,11,14,15} Others feel that prophylaxis may be considered on a short term basis but discontinued if there is no evidence of carditis or chorea after further evaluation.⁵ Further research is needed to clarify whether PSRA is merely a non-cardiac form of ARF, or if the two are entirely distinct entities. The need for antibiotic prophylaxis is an area of controversy in the literature at the present time and the choice to give prophylactic treatment differs depending on the clinician at the specific institution.

Discussion

It is still unclear whether PSRA represents an early or mild form of ARF or whether it is an entirely separate disease entity. Initial reports in the 1980s suggested that PSRA is a distinct entity from ARF.¹⁶ The main differences between the PSRA and ARF involves their presentation and response to treatment; these differences will be outlined below.^{5,15}

1. The latent period between the antecedent Streptococcal infection and the onset of PSRA is shorter (1-2 weeks) than the 3 to 4 weeks usually seen in classic ARF.
2. Patients with PSRA may experience a more prolonged course of polyarthritis (arthritis for 10-28 days and arthralgias persisting for 25-150 days).
3. The response of the arthritis to aspirin and other non-steroidal medication may be poor compared with the dramatic response often seen in classic ARF. Unfortunately, variations in the response to aspirin in such children often are not documented with serum salicylate levels and response to ASA cannot reliably be used as a diagnostic aid.
4. Evidence of carditis is not usually seen in PSRA patients.

The long term risk of RHD following PSRA has not been determined, although there have been several case reports of pediatric patients who have developed carditis with subsequent recurrences of PSRA.^{6,8,17} In past reports, it took as long as twenty years after the initial episode for these pediatric patients with PSRA taking no antibiotic prophylaxis to develop carditis or manifestations of RHD.^{2,6,8,10} More recently, silent carditis (documented carditis on echocardiography despite normal aus-

culatory and ECG findings) was reported in a pediatric patient who was previously diagnosed with PSRA.¹⁴ As of yet, the only reports of subsequent carditis after PSRA have been in pediatric patients. Recommendations to administer penicillin prophylaxis have only been made for adult patients with PSRA with certain characteristics, such as mitral or aortic valve disease, extra-articular symptoms, more than one episode of PSRA and first degree relative with history of ARF.¹² At this point in time, the clinical relevance of "silent carditis" is unknown and clinical evidence of carditis (See Table 1) and not silent carditis must be documented in order to fulfill the Jones criteria for a diagnosis of ARF.

Researchers have been searching for a link between these two diseases. It is presently thought that certain M serotypes of GABHS are "rheumatogenic" but it is unclear whether these particular serotypes are responsible for both ARF and PSRA.^{3,12,18} In addition, there may be human host factors which may make certain patients more susceptible to rheumatic complications after GABHS infections.^{3,11,12,18} There is also data suggesting a genetic link between PSRA and ARF, as these patients appear to share the same B-cell surface marker, D.^{8,17,19,20,21} An increasing body of evidence linking these two conditions as a single disease may help resolve the controversy regarding prophylactic treatment.

The carditis associated with ARF is one of the leading causes of acquired pediatric heart disease in North America and severe cases can result in congestive heart failure, the need for valve replacement or death.¹⁴ The recommendation for prophylactic antibiotics against streptococcal infections after ARF are clear, while the endorsement of this treatment following PSRA remains uncertain. Many remain reluctant to label children with PSRA and no cardiac disease as having ARF, and there is still no consensus about chronic penicillin prophylaxis for these pediatric patients.³ There truly is no recipe to follow as the guidelines vary depending on the case, the attending physician and the hospital site. In a recent review article, there was a marked discrepancy in treatment between different centers and among pediatric sub-specialists in infectious disease, rheumatology and cardiology.²² A few general suggestions for treatment follow.

- Look carefully to see if patient fulfills Jones Criteria for ARF. Patients with ARF without carditis (i.e. Fulfilling one major and two minor criteria) should be prophylaxed as recommended by the American Heart Association guidelines for ARF.
- For patients who do not fulfill criteria, the treatment should be individualized depending on the clinical situation. For example, a patient presenting with a severe migratory arthralgias (no arthritis) with fever, an elevated ESR and a prolonged symptomatic course may be a reasonable candidate for prophylaxis given that some experts in the field

consider severe migratory arthralgias as a major criteria for ARF. One should be more inclined to prophylax a patient who came very close to fulfilling criteria or who had recurrent episodes than someone who had a brief afebrile monoarthritis without any elevation of acute phase reactants.

- Other important factors that must be considered: is there the likelihood of recurrent strep infections? Are there school aged children in the family who will be bringing strep into the home? Has this patient had recurrent episodes of PSRA? Is there a strong family history of ARF? Is the family reliable and will they seek medical attention if their child has pharyngitis?
- An honest discussion with the parents presenting the risks and benefits of treatment should occur. The risk of carditis with PSRA is very very low, but not zero percent. Some families do not want to take even a small chance of developing carditis and opt for treatment, while others are comfortable waiting, with the understanding that as new information becomes available in the literature, the practice and recommendations may change.

PSRA seems to be part of the disease spectrum of ARF and therefore the use of prophylactic antibiotic therapy to prevent subsequent development of ARF and carditis in select cases should be considered.⁶ We are still unsure how often these

patients will develop later cardiac manifestations. Long-term studies are needed to delineate the current epidemiology of streptococcus related diseases, establish the relationship between PSRA and RHD and determine the long-term risk of carditis in patients with PSRA. Further genetic and longitudinal studies are needed to determine whether it is useful to distinguish between rheumatic fever and PSRA.¹² Finally, researchers need to assess the efficacy and appropriate duration of antibiotic prophylaxis of individuals with PSRA.¹⁴

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In the Literature: The *UTMJ* Club

Andrew Lustig, BSc (OT0), and
Sean Wharton, BScPhm, PharmD (OT1)

This section of the News and Views will present updates of recent advances in the medical, and scientific literature.

Cheer Up...Or Else! (Depression can Cause a Heart Attack)

A team at Johns Hopkins has found that clinical depression is an independent risk factor for coronary artery disease. The conclusion was derived from the Johns Hopkins Precursors Study, a prospective, observational study of 1,190 male medical students who were enrolled between 1948 and 1964 and who continued to be followed up. The men who reported clinical depression were at significantly greater risk for subsequent coronary heart disease, with a relative risk of 2.12 (95% confidence interval, 1.24-3.63) and myocardial infarction (RR, 2.12; 95% CI, 1.11-4.06). These data are not particularly surprising in light of the fact that several studies have found that depression is an independent predictor of poor outcome after the onset of clinical coronary artery disease. However, much less information was available concerning depression as a risk factor for the development of coronary artery disease.

Source: Ford et al. (1998). *Archives of Internal Medicine*. 158:1422.

Musically Talented Doctors are Better at Using Stethoscopes

A September 1997 study revealed that some physicians are not adequately skilled in the use of the stethoscope. Two researchers from Pennsylvania assessed the ability of first, second and third year internal medicine and family practice residents to detect 12 different cardiac problems by using a stethoscope. Interestingly, they found that physicians with the ability to play a musical instrument had a higher proficiency at detecting cardiac problems with a stethoscope. They also found that on average the residents recognized only 20 percent of the common cardiac problems that could be diagnosed using a stethoscope.

Source: Mangione et al. (1997). *JAMA*. 278:717.

Quit Smoking Now or You May Forget to Later (Alzheimer's and Smoking)

A study published in *The Lancet* found that cigarette smokers are more than twice as likely as non-smokers to develop Alzheimer's disease. The study was a population-based follow-up study of elderly people who were initially free of dementia. In total, 6,870 people aged 55 years and older agreed to take part. Smoking history was taken at baseline and participants were classified as never smokers, former smokers, and current smokers. During mean follow-up of 2.1 years, smokers had an increased risk of dementia (relative risk 2.2 [95% CI 1.3-3.6]) and Alzheimer's disease (RR: 2.3 [CI: 1.3-4.1]) compared with never smokers.

Source: Ott et al. (1998) *Lancet*. 351.

Crack Your Back to Get Rid of Your Asthma (Chiropractic Manipulation and Asthma)

Chiropractic manipulation has been reported to be of benefit in nonmusculoskeletal conditions, including asthma. A recent study attempted to determine the efficacy of this treatment. A Hamilton research group conducted a randomized control trial of chiropractic manipulation for children with mild to moderate asthma. Ninety one asthmatics were assigned to receive either active or simulated manipulation. After 2 to 4 months of therapy there was no significant difference between the two groups, although both groups demonstrated small increases in peak expiratory flow, improved symptoms of asthma and quality of life increases. It has been suggested that the improvements in both groups are due to a placebo effect, which includes patients receiving increased professional attention. Critics of this study address the concerns that a 2 to 4 month trial is not an adequate time frame to demonstrate the effects of manipulation. This debate will continue, as this is the first

RCT in the area of manipulation and asthma and further trials are necessary to support or refute these findings.

Source: Balon J *et al.* (1998). *NEJM*. 339:1013-20.

Less Blood is More

A recent Canadian randomized controlled clinical trial has reported that a restrictive strategy of red-cell transfusion is equally effective and may be better than the traditional liberal strategy. In this study, the liberal strategy consisted of transfusing patients whose hemoglobin dropped below 10g/dL (maintained at 10-12 g/dL) and the restrictive strategy consisted of transfusing when hemoglobin dropped below 7g/dL (maintained at 7-9g/dL). Hebert *et al.* have reported in *NEJM* that overall 30-day mortality rates were similar in patients given the liberal or restrictive strategy. The restrictive strategy was shown to lead to decreased mortality in patients who were in-hospital, who were less acutely ill or who were less than 55 years of age. However, in patients with clinically important cardiac disease the restrictive strategy was more detrimental in terms of mortality. Source: Hebert *et al.* (1999). *NEJM* 340:409

What Makes an Excellent Physician Role Model

Wright *et al.* have evaluated specific attributes of excellent medical role model within the internal-medicine house staff at four teaching hospitals. Physicians who spend more than 25% of time teaching, who spend more than 25 hours weekly teach-

ing, who stress the importance of the doctor-patient relationship in their teaching, who teach the psychosocial aspects of medicine and/or who have served as chief-resident were found to have a higher likelihood of being rated as excellent role models. These results indicate that a number of characteristics that are associated with excellent role models can be acquired by modifying teaching practices and behaviors.

Source: Wright S.M. *et al.* (1998). *NEJM*. 339:1986

Toronto Investigators Reveal Causal Link between Chlamydia and Heart Disease

Until recently, heart disease had been linked epidemiologically to infection with *Chlamydia* but the rationale for this relationship remained elusive. Bachmaier *et al.* have recently shown that a chlamydia-derived outer membrane protein found in *C. pneumoniae*, *C. psittaci* and *C. trachomatis* share sequence homology with the α -subunit of the heart specific myosin heavy chain. Injection of these bacterial peptides into mice with the appropriate inflammatory stimulus induced an autoimmune inflammatory heart disease with perivascular inflammation, fibrotic changes, and blood vessel occlusion in the heart. This study strongly indicates that molecular mimicry between bacterial antigens and heart muscle proteins exists and may lead to an inadvertent immune attack on the heart as a by-product of immunity against chlamydial infections.

Source: Bachmaier *et al.* (1999). *Science*. 283:1335

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UTMJ Series on Complementary and Alternative Medicine (CAM)

Part 2: Herbal Medicine

Rahel Ahmed, BSc. (OT1), and Luke Bui, BSc. (OT1)

Herbal medications are the most popular therapeutic intervention on a worldwide basis and have recently received increased attention in North America. According to one estimate, 33% of Americans use herbal medication. While there has been a recent surge of interest, herbal medicine is an ancient form of healing that dates back to the Stone Age.¹ In North America, herbal medications are prescribed primarily by non-allopathic practitioners, such as herbalists, naturopathic doctors and traditional Chinese doctors. Due to its popularity with the general public, it is not surprising that physicians, medical students, and other health care professionals have indicated that they require more knowledge in the field of herbal medicine. This article, the second of a three part series on CAM, will present an overview of herbal medicine and relevant health issues.

What is Herbal Medicine?

Herbal medicine is the use of natural plant substances, in the form of teas, extracts or pills, to treat illness.^{1(a)} Herbs are the primary therapeutic agents for 80% of the world's population.² Also known as phytomedicine, the use of plants for healing is an ancient practice. Various systems of traditional healing use herbal products, including traditional Oriental medicine, Ayurveda, Shamanism, Native American healing and Tibetan medicine. Many modern drugs such as atropine, codeine, colchicine, digoxin, and morphine are derived from plants, while drugs such as lovastatin and cyclosporin are derived from fungal sources.^{3,4} According to one estimate, there are 117 licensed medications derived from natural plant derivatives



Teddy Cameron

used globally.³ More recently, the use of some anti-cancer plant derivatives for treatment of advanced-stage cancers has shown promise, such as vinorelbine for non-small cell carcinoma of the lung and paclitaxel for ovarian carcinoma.^{5,6} Popular herbs such as ginkgo, ginseng, St. John's Wort and echinacea, are used for everything from improving memory to treating the common cold.

Who Uses Herbal Medicine and CAM Therapies?

Compared to North America, many European countries are more familiar with complementary and alternative medicine including herbal medications. In Germany, physicians commonly prescribe herbal medication. For some illnesses, herbal medicines are preferred over prescription drugs as a first line of treatment. In North America, physicians have been reluctant to use CAM, although there is a significant proportion of the Canadian public using herbal medicine and other CAM therapies. According to recent statistics, 20% of Canadians claimed to have used some form of CAM therapy. The Canadian market for herbal medicines was valued at \$150 million in 1995, up 25% from 1994, and growing steadily at 15% per year.^{12b} The projected value of the Canadian herbal market for 1999 is \$260 million. In the US, sales of herbal medicines was \$2.5 billion in 1996 and growing 25% per year.⁹ The 1994-95 National Population Health Survey found that for Canadians age 15 and over, high income earners, those with higher education, and those with multiple chronic diseases had the highest proportion of alternative practitioner consultations.⁷

The Allopathic Physician and Herbal Medicines

The rise in use of herbal medicines has added to the list of questions a physician must ask during history taking for any ailment. Herbal medicines are believed by many consumers to be more 'natural'. However, the belief that 'natural' implies absolute safety is dangerous and potentially fatal. To provide an acceptable standard of care, physicians must have an awareness of common adverse effects associated with herbal use and misuse, especially if the physician suspects the use of herbal medication. Common adverse effects include drowsiness, dizziness, diarrhea, and vomiting (Tables 1, 2). In addition, there are several documented drug-herb interactions (Table 3). Due to the possibility of drug-herb interactions and herb-disease interactions, physicians need to ask patients, especially those that are more likely to use CAM therapies, if they are taking any herbs. Physicians should also be aware of some common medical conditions associated with the highest use of CAM therapies. These include back problems, allergies, arthritis, insomnia, sprains or strains, headache, high blood pressure, and digestive problems.⁸ Alarmingly, more than 70% of those who use CAM therapies do not report it to their family physician.⁸ Eisenberg *et al.* cited a deficiency in current patient-physician relations as the cause.⁸ It is clear that in

order to provide an acceptable standard of care, physicians need to know what herbs their patients are taking, their potential side effects, and possible drug-herb interactions.

Table 1
Common Adverse Effects Resulting from Use of Herbs
(in order of frequency)

Drowsiness/Dizziness
Diarrhea/Vomiting
Abdominal Pain
Nausea
Cardiac Rhythm Disturbances
Agitation/Irritability

Adapted from Shaw D, et al. *Traditional Remedies and Food Supplements*.²⁰

Commonly Used Herbs

Table 2 presents a list of selected herbs and their stated benefits and side effects.¹⁰ There are estimated to be over 1400 herbs in use today.¹⁰ The table focuses on a few of the more well-known herbs. Only nine herbs are approved by the US Food and Drug Administration for selected applications.¹⁰ The most popular herbal medications in use are ginseng (20% of herbal medications taken), garlic preparations (18%), and ginkgo (10%).¹¹

Scientific Support for Herbal Medicines

Scientific evaluation of herbal therapeutic properties is needed to substantiate many of the claims currently prevalent. Ideally, herbs would be evaluated in randomized controlled trials.¹² Some herbal medications have been scientifically proven to have clinical therapeutic advantages over conventional drug therapy in the treatment of disease. Saw Palmetto extracts have been evaluated as treatment for benign prostatic hyperplasia.¹³ Saw Palmetto produces improvements in urinary tract symptoms and urinary flow, in a manner similar to finasteride, a drug normally used for this purpose. Furthermore, this herb is associated with fewer adverse treatment events than finasteride, indicating that in this case a herbal medication may be preferred to conventional treatment.

Erroneous claims of benefits of certain herbs have been disproved by clinical evaluation. Laetrile (amygdalin) is a substance found in the pits of peaches, almonds, and apricots. Since the 1920s, it had been thought to kill cancer cells. A clinical cancer trial in 1982 showed that laetrile did not alleviate symptoms or slow the course of disease, and therefore was not a suitable treatment for cancer.¹⁴ In other studies, the scientific literature may offer conflicting accounts of an herb's properties. Garlic has a reputed ability to slow down the process of atherosclerosis. Two sets of reviewers stated that there was no evidence to suggest that garlic was an

Table 2
Summary of Selected Herbs and Their Properties

Common Name	Popular Laypress Claims	Scientifically Tested Properties	Adverse Effects/ Warnings
Aloe (Aloe Barbadensis)	Emollient, laxative, minor burns, insect bites, skin irritations, minor cuts, wrinkles, regulates liver function, PMS, emmenagogue (menstrual regulation)	FDA approved as a laxative	May bring about abortion or premature birth; loss of electrolytes with chronic use
Echinacea (Echinacea augustifolia, E. pallida, E. purpurea)	Antiseptic, digestive, eczema, acne, migraine, antipyretic, antifatulent, wound healing, immune stimulant to help fight colds, influenza immune-stimulant effect	allergies (infrequent)	St. John's Wort
(Hypericum perforatum)	Antidepressant, anti-inflammatory, antidiarrheal, astringent, rheumatism, gout, diuretic, gastritis astringent, mild antidepressant effect	possible antiviral action	Photosensitization, dermatitis
Garlic (Allium Sativum)	Antihelmintic, antispasmodic, diuretic, carminative, digestive, expectorant, treatment of atherosclerosis and high blood pressure, blood clotting disorders	garlic appears to provide some protection against atherosclerosis and stroke and may reduce blood cholesterol and blood pressure allergic reactions; reduction of clotting time;	consumption of >5 cloves/day may cause heartburn, flatulence
Ginkgo (Ginkgo biloba)	Enhanced cerebral blood flow, tinnitus, vertigo, Alzheimer's disease, hemorrhoids, slows aging process, prevents cancer, antidepressant, improves memory	gingko promotes vasodilation and improved blood flow in arteries and capillaries; acts as a free radical scavenger	GI disturbances, headache, allergic skin reactions, restlessness
Ginseng Panax ginseng (Oriental), Panax quinquefolius (American), Eleutherococcus senticosus (Siberian ginseng)	Adaptogen, demulcent, cure-all, antistress agents, aphrodisiac, menopausal symptoms, reduces cholesterol, increases energy, inhibits tumours	solid clinical data is lacking although some studies have shown some beneficial pharmacologic effects	insomnia, diarrhea, skin eruptions, menopausal bleeding
Saw Palmetto (Serenoa repens)	Diuretic, BPH, urinary antiseptic, aphrodisiac, GI infections, increase breast size, increase sperm production, reverse atrophy of testes and mammary glands has antiandrogenic properties and may have anti-inflammatory actions	banned as a drug in the US by the FDA	not available
Goldenseal (Hydrastis canadensis)	Bitter tonic, digestive aid, genitourinary conditions, menorrhagia, upper respiratory ills, irritated gums, canker sores, ringworm treatment, atrophic vaginitis	this herb may have some astringent and weak antiseptic properties but there is no scientific evidence to support claims	no safety or efficacy data available when this herb is used internally

Adapted from Youngkin, EC, and Israel, DS. (1996) A Review and Critique of Common Herbal Alternative Therapies.

Table 3
Possible Drug-Herb Interactions

Herb	Drug-Herb Interactions	Clinical Effects
Echinacea	Hepatotoxic drugs (anabolic steroids, amiodarone, methotrexate, Ketoconazole)	hepatotoxic
Feverfew	Warfarin	alter bleeding time
Garlic	Warfarin	alter bleeding time
Ginkgo	Warfarin	alter bleeding time
Ginger	Warfarin	alter bleeding time
Ginseng	warfarin, phenelzine sulfate, estrogens, corticosteroids, digoxin	alter bleeding time, tremulousness, manic episodes
St. John's Wort	Monamine oxidase inhibitors, selective serotonin reuptake inhibitors	theoretical interaction at serotonin receptors, unstudied (unknown effect)

Adapted from Millar L. Herbal Medicinals. Arch Intern Med. 1998;158:2200-2211(21)

effective lipid-lowering agent.^{15,16} However, results of a meta-analysis suggested that daily ingestion of fresh garlic significantly reduced total cholesterol levels.¹⁷

Regulation of Herbal Medication

Issues concerning dangers of using herbal medication include quality control, toxicity, allergies and adverse drug-herb interactions. Many herbs are sold as foods, according to the Canada Foods and Drugs Act.¹⁸ Consequently, proof of efficacy and labeling of side effects are not required. Labeling of an herbal remedy's ingredients may be misleading or nonexistent. Additionally, some herbal medication may in fact contain contaminants.¹⁹ A 5-year study on toxicology of traditional medication has shown liver problems following the use of Chinese herbs for skin disorders, allergic reactions to royal jelly, and heavy metal poisoning caused by herbal medication from India.²⁰ Patients with allergies to ragweed should avoid teas made from golden rod, marigold, yarrow, St John's wort and chamomile.²¹ Consideration of possible drug-herb interactions is needed when physicians are prescribing drugs (Table 3).

Current Regulation

Presently, there is limited regulation of the quality of herbal medication in Canada. Many herbal medication have been classified by the *Canada Food and Drug Act* as foods, and therefore are not subject to the same degree of regulation as drugs.¹⁸ Since July 1, 1997, all herbal medication, manufactured and imported, have been required to have a license indicating that standards of quality, cleanliness, and labeling are met.¹⁸ The Standing Committee on Health (SCH) was created in 1997 to perform a full public review of the legal regime governing natural health products (NHP). NHP's include Traditional Chinese Medicines, Ayurvedia, Native North American Medicines, homeopathic preparations, and vitamin and mineral supplements. The latest report by the SCH in November 1998 established a framework regarding the legalities of herbal medication use. Recommendations include creating an expert and regulatory structure to evaluate claims and safety of herbal medication, quality control guidelines, efficacy, product licensing, and labeling. It is interesting to note that according to the new SCH report, claims of efficacy can be established by three different methods: double blind clinical trials, the success of traditional practices, or by professional consensus. This is contrary to allopathic medications which require strict clinical trials to establish efficacy as determined by Health Canada. This approach to license complementary medications based on non-scientific evidence is practical for the public and the industry producing these agents, as neither group would be comfortable with a 10 year delay in order to conduct clinical trials. Many experienced non-allopathic practitioners already consider these agents to be safe and recognize that they have an established record in other countries. While this approach may be practical, it is still concerning.

Anecdotal studies from other countries may not be valid in North America and may not have involved combining these drugs with current medications. Only time will determine whether this is an appropriate manner in which to establish a drug schedule for complementary medications.

Conclusions

The use of herbs is an ancient and culturally based practice. The herbal medicine industry is growing, and regulation of herbal products in Canada is emerging. Today, many people use herbal medication for a variety of conditions ranging in severity. Despite the often conflicting reports in the literature, physicians must make an effort to become educated on several aspects of herbal medicines' uses and effects. There are common adverse symptoms associated with herbal use and misuse, and physicians should be aware of them. When talking to patients, physicians should keep in mind that the majority of patients do not report herbal use to their physicians, and that potential dangers of contamination, toxicity, allergies, and adverse drug-herb interactions exist. Since the use of herbs is traditional in many cultures, a non-judgmental approach by physicians may foster open communication with patients and promote health.

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Academic Freedom Under Corporate Fire

(A Commentary on the Nancy Olivieri Story)

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The following commentary contains opinions of the author and does not necessarily reflect the opinions of the *UTMJ* or any members of the editorial board.

To study, to Finish, to Publish.

- Benjamin Franklin

Much has been written and debated regarding the recent struggles of Dr. Nancy Olivieri and the pharmaceutical company Apotex Inc. The rancor that has evolved has caught the attention of not only the medical community and media, but also the general public and has raised important concerns about the increasingly common relationship between medical research and the pharmaceutical industry that provides much of the necessary funding.

With more and more research at Canadian institutions and hospitals being fueled by support from pharmaceutical companies, concerns about the maintenance of patient safety and the academic freedom to publish have moved to center stage. This has become an even greater concern in the face of declining per-capita public funding for health research in Canada, a situation that has allowed more private funding into the medical research arena. Commercial funding reached \$825 million in Canada in 1992 and has been increasing throughout the 1990's. Although this funding is crucial to the continuance of medical research in this country, there arises the potential for conflicts of interest, especially when the financial support comes from companies that have a vested interest in the results of trials involving their drugs. This trend, if left unchecked, could progress to the point where patient safety becomes compro-

mised. Further, there is also the concern that the private sector could directly influence the publication of important scientific data that, if left unpublished, could put patients' lives in jeopardy.

The most recent controversy revolves around Dr. Nancy F. Olivieri. The world renowned haematologist and researcher of the blood disorder thalassemia is at the forefront of research into iron chelation therapy for patients afflicted with this disease. Thalassemia patients need routine, life saving blood transfusions to provide them with functioning blood. Unfortunately, as a result of these transfusions, a life-threatening situation soon arises due to the deposition of excess iron in major organs of the body such as heart, liver, pancreas, and pituitary. Therefore, it is crucial to administer an iron chelating drug to rid the body of this excess iron in order to limit toxicity. Until recently, the drug of choice for iron chelation had to be administered via slow, subcutaneous infusion for a 12-hour period nearly every day of the patient's life. As a result of this uncomfortable administration schedule, much attention had been focused upon developing a less invasive, less painful means of administering an iron chelator. This potential was realized when an orally-active experimental compound in Britain was found to chelate iron and excrete it in the urine, offering thalassemia patients all over the world the hope of a more bearable means of treatment.

After an initial 3 year trial of this drug, called L1 (Deferiprone), a multi-center team of researchers, including Dr. Olivieri, demonstrated that the drug produced the desired effect and progressively decreased levels of iron in twenty-one patients.

These results were published in 1995 in the *New England Journal of Medicine*.¹ Despite the early promising results, it was still necessary to study the efficacy and safety of this drug in a larger study involving other countries as well as North America. Enter Apotex Inc., a Toronto-based pharmaceutical company that was previously a manufacturer of generic drugs but was aspiring to develop, license, and market its own drugs. Apotex Inc., which markets Deferiprone in Canada, agreed to finance a study in young thalassemia patients in Canada, the United States, and Italy for 2 1/2 years, at a cost of \$120,000 per year. The study was also partially funded by the Medical Research Council of Canada.

The key point to this story, and the controversy that has ensued (for a summary, please refer to Yiu)², is the signing of a confidentiality agreement by Olivieri which stipulated that any data generated from the multi-centered trial would be the property of Apotex Inc. In other words, she would need the company's permission to publish any data regardless of any potential hazards that may be caused by the administration of Deferiprone. Once Olivieri discovered that Deferiprone was causing serious side effects, she immediately informed her patients and their parents. The response from Apotex was swift. Olivieri was discharged as chairperson of the study's steering committee and was threatened with legal action should she continue to inform patients and/or publish what Apotex called "misinformation" regarding their drug. Despite these threats, Olivieri proceeded to publish her results in the August 13, 1998 edition of the *New England Journal of Medicine*.³ In the months that followed, there developed a fierce and publicized battle with Apotex Inc. and an escalating controversy regarding the relations between Olivieri and the Hospital for Sick Children. Largely because of the pressures of fellow researchers and physicians at HSC, an external inquiry, directed by Dr. Arnold Naimark, was established to investigate the case. On January 6, 1999, nearly five months after the original article was published in *NEJM*, Dr. Olivieri was relieved of her duties as head of the hemoglobinopathy program at HSC due to "personal reasons". However, due in large part to the diligence of University of Toronto administrators and other mediators, Olivieri and HSC established a new settlement just nineteen days later. It would seem that the ongoing dispute is, at least temporarily, resolved.

A similar case involves Dr. Betty Dong,^{4,5} a researcher at the University of California at San Francisco, who, in 1987, agreed to collaborate with Boots Pharmaceuticals Inc. to test a thyroid drug, levothyroxine (Synthroid), which was manufactured by Boots. Boots was optimistic that Dr. Dong's results would demonstrate that Synthroid was not equivalent to its generic counterparts, since her previous research had indicated a trend in this direction. Demonstrating inequivalence with generic

brands would ensure that Synthroid would monopolize the levothyroxine market. As expected by most pharmacology researchers, Dr. Dong's results demonstrated that the generic brands of levothyroxine were bioequivalent with Synthroid. These results were not received favorably by Boots. Although Dr. Dong sent her manuscript to the *Journal of the American Medical Association* in November of 1994, she abruptly withdrew it in January of 1995 citing her reasons to the journal as "impending legal action by Boots Pharmaceuticals Inc. against the University of California, San Francisco (UCSF), and the investigators". The reason for the legal action was that Dr. Dong had signed a protocol contract stipulating that all data obtained by the investigator would be considered confidential and was not to be published without written consent from the pharmaceutical company. Because of this clause Dr. Dong was advised by UCSF to withdraw her paper and was informed that UCSF would not defend the authors should the case be brought to trial by Boots/Knoll. To make matters worse for Dong, an article by Mayor *et al*, employees of Boots and Knoll Pharmaceuticals, was published as a reanalysis of Dong's study. It cited "major study limitations" that, if addressed, would have revealed that the therapeutic preparations of the generic and brand-name drugs were indeed inequivalent. As a result, Synthroid's position would be strengthened. Further, the article was published in the *American Journal of Therapeutics*, which is co-edited by Mayor, thus preventing any journal from publishing Dong's data in the future. However, the Food and Drug Administration informed Boots/Knoll that the article was misleading and advised that their view should not be further disseminated. Under pressure from the FDA, and realizing the potential for negative public perception of its actions, Boots/Knoll began negotiations with UCSF. This eventually led to an agreement that Boots/Knoll would not block the publication of the manuscript by Dong *et al*⁴ despite maintaining their stance that the conclusions of the study were not supported by the data obtained.

The cost of taking a stance against a research sponsor is equally evident in the case of Dr. David Kern, an occupational-health specialist at Memorial Hospital in Pawtucket, R.I. He too signed a non-disclosure contract prior to commencing his investigation into the prevalence of lung disease in employees of textile manufacturer Microfibres Inc. in 1994. The results indicated that there was indeed an increased incidence of lung disease in employees of the textile company. Kern has met strong resistance in his attempts to publish the results not only by the company, but also by his employing hospital and by Brown University, his academic affiliate. Although he has received some support from colleagues, Kern's contract as director of the Occupational and Environmental Health Service at Memorial Hospital was subsequently not renewed this year, and the occupational health program at Brown, which he

directed, was terminated soon after he presented his results. A spokesman for Microfibres Inc., John Woodhouse, stated that Kern's research methods did not comply with his contract. Further, the company was concerned that Kern would release company trade secrets, such as lists of chemicals that might have had a causative role in the development of the disease. Although his case has gone to a labor review board, Kern has little hope that they will come to decide in his favor.

These three scenarios highlight the seriousness of the potential compromise of academic freedom. There is much at stake here as the influence from the corporate sector continues to creep its way into the sacred realm of scientific objectivity. At the crossroads is the researching physician who is caught between the pressures of the corporate financial life-line and the maintenance of the best interests of patients. We as medical students and physicians are bound by an oath and conscience to uphold the virtues of our respected profession; our mission to safeguard the health of all people is what defines us and is part of the truth of our existence as physicians and advocates of healthy public policy. Aligning with this philosophy are recommendations put forth by the World Medical Association's Declaration of Helsinki⁶ which are in place to ensure the safety of human subjects involved in biomedical research.

The Helsinki Declaration stipulates:

"every biomedical research project involving human subjects should be preceded by a careful assessment of the predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society".

Further,

"in any medical study, every patient – including those of a control group, if any – should be assured of the best proven diagnostic and therapeutic method, the advantages of which must be weighed against the potential benefits, hazards, and discomfort of new treatment options".

However, the advent of a new player, the private industry, throws a potential ethical wrench into the mix. Dr. Olivieri's is only the latest of other recent high profile examples of this disturbing trend. The cases of Dr. Dong, Dr. Kern, and Dr. Olivieri have inherent similarities. In each, there is a scientific argument in favor of the meaning of the data obtained. As well, they are all examples of research that was deemed scientifically sound by a stringent peer-review process, and which was eventually made public and posed an immediate threat to the respective industrial corporations involved. Each case revolves around sound scientific work, not only because it passed peer review, but also because it survived the prolonged scrutiny of their respective affiliate

institutions. The real question is whether those conducting medical research should sign agreements that prevent them from disseminating their findings to patients and the general public. In that regard, there is a need for legislation in the United States and Canada that would ensure the freedom of peer-reviewed scientific expression. In the end, this would ensure that potentially dangerous treatment can be made known and arrested before patient safety becomes an issue.

It is more important that clinicians report negative results so that they can use the information to better serve their patients. It is shockingly apparent, however, that this theme of being forced to withhold negative results is probably more common than generally suspected. Blumenthal *et al.*⁷ has published a report outlining the prevalence of withholding research results by researchers. They report that approximately 20% of 2,100 life science faculty reported a delay of greater than 6 months in the publication of their results. Of these, 28% of the researchers believed the delay was to "slow the dissemination of undesired results". Although Blumenthal *et al.* concluded that withholding results was not widespread, workers at Carnegie-Mellon University in Pittsburgh, PA report more evidence of this.⁸ In their report, 35% of university-industry research centers signed agreements that allowed the sponsor to delete information from publications; 53% allowed the publication to be delayed outright. If the private sector is not influencing results, then it is reasonable to suspect they are influencing the investigators themselves, either directly or indirectly.

It is important to take a step back at this point and visualize the big picture of what has ensued in the above cases, in particular that of Dr. Olivieri. Putting aside personal opinions regarding the controversy itself, one must admire and applaud the resolve and courage that Dr. Olivieri has projected in the midst of the quagmire of her legal battles and scientific persecution. She has demonstrated unwavering scientific integrity and objectivity, qualities in a researching physician that form the fundamental basis of credible medical investigators and permit the acceptance of new scientific truths. In addition, her fellow researchers and physicians who, in response to their colleague's professional and personal battles, revolted and stood united next to her in a strong and convincing show of solidarity are to be applauded. And, above all, her unqualified dedication to protect the best interests of her patients by informing them of the hazards of a drug that they previously believed was free from any adverse effects is to be praised.

Indeed, there is no denying the fact that honest and open partnerships between industry and academic institutions

are important alliances that must be maintained to ensure future productivity from Canadian research centers. This is especially true considering the suboptimal public funding currently available for medical research. Regardless of the results, it is the duty of all researchers to publish their objective and credible medical findings and to recognize and avoid any attempts to suppress what is recognized to be scientific truth. Finally, we must always ensure patient safety and the fight for the freedom to make known important scientific findings that have direct influence on medical treatment. These are the issues we must covet and remember throughout our careers as guardians of the Hippocratic Oath, which demands that we "do no harm" to our patients. In this regard, it is Dr. Olivieri's persevering commitment to ensure that her patients came to no harm, despite facing professional and personal scrutiny, that we should reflect upon in our own future interactions with our patients and the industry.

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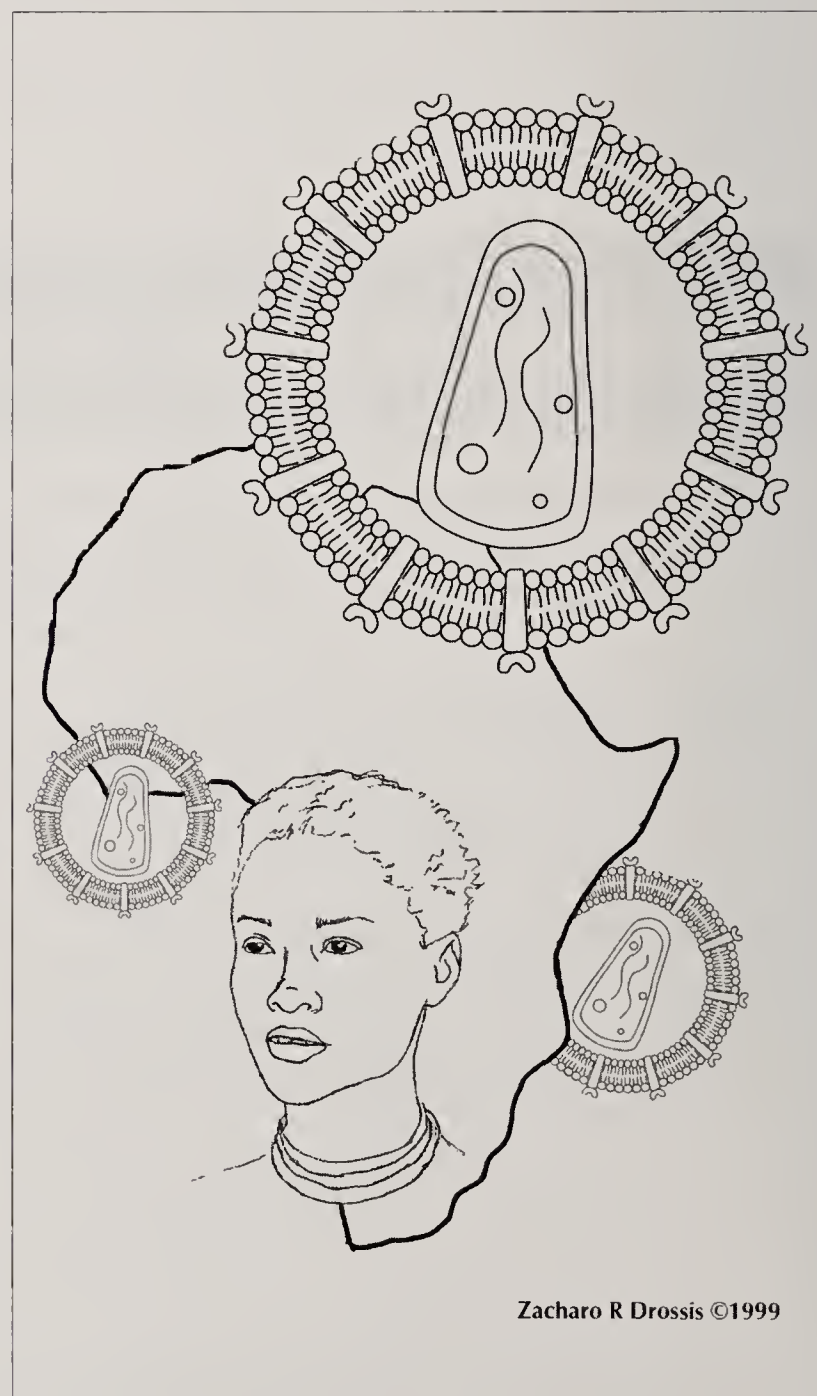
Emilia Jumbe, MBGh.B,* and Dale Needham, MAcc., GA, MD**

Abstract

In sub-saharan Africa, a region where up to one-third of urban adults are infected with the human immunodeficiency virus (HIV), communication is critically important in caring for patients. However, through elective experiences in Africa and Canada, we have come to appreciate the difficulties of such communication. Patient characteristics, the socio-economic and cultural environment, HIV-specific issues and physician-related factors are all potential barriers in effectively communicating with patients. These types of issues are also relevant considerations for communication within the Canadian setting.

A physician should be able to easily explain the relevant aspects of any medical condition to their patient without losing the context or importance of the message. In a region where up to one-third of urban adults are infected with the human immunodeficiency virus (HIV), such communication and empathy is critically important in caring for patients. Communication is a part of health care delivery that requires few financial resources, but has important benefits in patient care. Unfortunately, this communication is often lacking within African health care settings. This is one of the harsh, and often overlooked, realities of health care delivery in Africa.

Completing electives as part of medical school education has allowed physicians to experience health care delivery in Canada and several other settings in Africa. This has provided a unique opportunity to view African health care from a Canadian perspective, and to view Canadian health care from an African perspective. This dual viewpoint allows for interesting observations regarding HIV. It is our hope that these experiences



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and reflections may help create increased awareness of the importance of communication with patients.

Due to fundamental differences in patients' knowledge of health issues in Africa, communication regarding disease is very different from Canada. Most patients in Africa, when encountering a new diagnosis do not have any prior understanding of their ailment. They are fully dependent on the medical staff to provide basic education and to correct numerous cultural myths about their disease. However, the high esteem with which patients view medical staff often intimidates them and consequently, they are loath to ask questions for fear of conveying less than full faith in their health care provider. This environment results in some patients remaining in hospital beds for days or weeks without ever knowing why they are there. This need for communication is especially important with HIV.

Informing a patient that his or her disease is due to HIV infection is difficult in any setting. In fact, even among African medical staff, the word HIV/AIDS is often avoided. Instead euphemisms such as retroviral disease (RVD), lymphotropic disease, or ELISA (Enzyme-Linked Immunosorbent Assay, the laboratory technique commonly used to diagnose HIV) are used to avoid stating the obvious diagnosis. This lack of communication can impact on patient care. In one instance, Zambian medical students were having teaching rounds with a patient who had molluscum contagiosum infection of his genitals. During these rounds, the senior doctor mentioned that currently this condition is almost exclusive to HIV positive patients. Unfortunately, the 25 year old man was not aware of this. When HIV was openly mentioned his expression revealed immediate shock. Noticing this, the senior doctor tried to falsely ease his mind by saying not everything mentioned in the rounds related to him. At the end of rounds, the clinical clerk caring for this patient needed to be more honest with the patient regarding the previously avoided issue of HIV.

Communication is also difficult because of the social implications attached to HIV. In sub-Saharan Africa, HIV is predominantly transmitted through heterosexual sex. Consequently, once a man is diagnosed with it, he is labeled "promiscuous". It is then accepted that his spouse is HIV positive and the community starts to talk about his "poor wife" and socially stigmatize the entire family. These social judgments make it very difficult for a family to learn of an HIV diagnosis.

There are also significant barriers in openly talking about death. When dealing with a healthy looking HIV-positive patient it is often very difficult to convey the potentially fatal consequences of this disease. Thus, few doctors try. In many ways, it is easier for a doctor to reveal to a patient that he may be dying when he looks or feels ill. Furthermore, some doctors do not mention the underlying disease despite complaints from the patients' family that the patient is not improving.

A similar difficult situation also occurs with discussions of sexual behaviour. It is only recently that issues surrounding sex could be discussed without being culturally insensitive. Previously, matters of sexual education had been delegated exclusively to a specific elder in the family. As the AIDS death toll rises, families have begun to realize that one cannot talk about HIV/AIDS without

discussing sex, and slowly this tradition has begun to change.

In addition, the majority of patients admitted to the medical wards in sub-Saharan Africa suspect they are HIV positive. Given its bleak prognosis, many patients simply do not want their HIV status confirmed. Physicians must struggle with patients' own denial of this disease. For example, a healthy-looking, intelligent 31 year old professional male was seen in the surgical clinic at University Teaching Hospital, Zambia. Clinically, he had a Kaposi's Sarcoma lesion on his slightly edematous left leg. The visiting consultant surgeon agreed with the diagnosis and advised that the patient be informed of the association of Kaposi's Sarcoma with HIV, especially in the Zambian setting. The patient, however, did not want such confirmation of HIV. Instead, he chose to await the outcome of chemotherapy for the Kaposi's Sarcoma, and only if it reappeared would he consider having an HIV test.

Beyond these serious communication issues remain many other barriers in managing HIV-positive patients in Sub-Saharan Africa. Physicians must struggle with their own denial and sense of impotence when working in Africa. A single day in an HIV clinic in Canada gives insight into the growing gap in HIV therapy between resource-rich and resource-poor countries. Seeing an HIV patient in North America without opportunistic infections, a CD4 T-cell count of 540, and a HIV plasma viral load below the threshold of detection testifies to the impact that HIV therapies can have on patients' quality and length of life. However, this standard of care in the monitoring and treatment of HIV is not available in Africa. How can we explain to patients the importance of plasma viral load and CD4 T-cell counts as prognostic indicators when the tests to measure them are not available? Moreover, the annual per capita health budget of many African countries would only buy a few tablets of zidovudine (AZT). Most patients' annual income would not even purchase a two week supply of these medications. It is difficult to face these patients living with HIV infection and know that there is little treatment we can offer to help with this disease. This brings forth many poignant questions. What good will be done in sharing the obvious diagnosis in this setting when it often results in patients prematurely giving up on life? As most patients say, "Why would I want to live knowing I will soon die when I could live without knowing my status and hope for life?" When most do not modify their sexual behaviour, what are we doing to improve the patient's quality of life by sharing the diagnosis? How can we cope with trying to counsel so many patients? Through these difficult circumstances, we understand how it seems easier to join the patient in denying HIV infection.

The shared experience of medical electives in Africa and Canada provide different ways to think about HIV-related communication in Africa. Patient characteristics, the socio-economic and cultural environment, disease-specific issues, and physician factors are all key in better understanding patient communication. These factors are also equally relevant when considering communication issues around HIV and other diseases in the Canadian setting. After these electives, we have both returned to our countries and more familiar medical settings to face these challenges as new doctors. We hope that our recent experiences will help us to better communicate with patients and families throughout our internship year.

Breathless

Ra Han, BSc. (OTO), Mark Benaroia, BSc. (OT1), and
C. Maria Bacchus, MD, FRCPC, MSc.*

Comment from the editors:

Please direct any questions or comments about the case to the editors at the following email addresses: m.benaroia@utoronto.ca and ra.han@utoronto.ca. We invite any clinician who has a case of educational value and who is interested in contributing to the UTMJ to contact the editors at the same email addresses above.

The Scene

A conference room in a Toronto teaching hospital. Students, residents, and staff physicians are seated around a conference table. Amit, a third year medical student, Jill, a fourth year medical student, Michael, a first year resident (PGY1), and Nava, a second year resident (PGY2), have worked overnight, admitting patients to their team at the hospital. They have selected a case from the previous night's admissions, which Amit will now present to the group. A faculty member, Dr. Koo, will facilitate a discussion of the case.

Amit: This is a 68-year old female with a known history of breast cancer who presented to the Emergency Department with a chief complaint of shortness of breath.

Dr. Koo: Let's pause here. Clinicians usually begin to formulate a differential diagnosis after hearing the chief complaint. Jill, what diagnosis do you consider when you hear a history of dyspnea?

Jill: The differential diagnosis for dyspnea can be approached using the broad categories of cardiac disease, pulmonary disease, and other. Common respiratory causes of dyspnea include asthma, emphysema, pneumonia, pulmonary emboli, lung cancer and pneumothorax. Important cardiac causes of dyspnea include congestive heart failure, myocardial infarction

and pericardial disease. In addition, other conditions such as anemia can lead to dyspnea. Dyspnea may also be associated with anxiety attacks.

Dr. Koo: Thank you, Jill. That's a very good approach to dyspnea. The differential diagnosis for dyspnea is quite extensive. Michael, given what we already know about this patient, can you focus the approach a bit more?

Michael: Given that she has a history of breast cancer, I would wonder if her dyspnea is related to her underlying illness.

Dr. Koo: That's an excellent thought, Michael. Amit, can you think of how breast cancer can present with respiratory causes of dyspnea?

Amit: Breast cancer can be complicated by pleural effusions, pulmonary emboli, pneumonia and lymphangitic spread. Some chemotherapy agents such as methotrexate can also cause pulmonary fibrosis. In addition, radiation therapy can cause acute pneumonitis.

Dr. Koo: Jill, can you discuss other reasons why this patient may be dyspneic in relation to her history of breast cancer?

Jill: Breast cancer can also metastasize to the pericardium and pericardial effusions and tamponade can present with dyspnea. Radiation could result in constrictive pericarditis. Chemotherapy with anthracyclines, such as adriamycin, can also result in a dilated cardiomyopathy.

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Dr. Koo: Those are all very reasonable approaches. From a very broad initial differential diagnosis, we can narrow our diagnostic possibilities if we are to relate it to her history of breast cancer. However, it is important to note that her dyspnea could be unrelated to her breast cancer.

Amit, can you give us some more information about this patient's dyspnea?

Amit: Her dyspnea began suddenly while reading. It was associated with non-radiating, constant, sharp, right-sided chest pain which increased with inspiration. There were no alleviating factors. The pain was not affected by position or exertion. There were no associated palpitations, presyncope, syncope, nausea, diaphoresis, cough, fever or hemoptysis. She had never experienced similar episodes in the past.

Dr. Koo: With this additional history, what do you think the most likely diagnoses are? Michael?

Michael: The description of dyspnea with associated pleuritic chest pain is most suggestive of pulmonary embolus. Dyspnea is the most common presenting symptom. Pleuritic chest pain, cough, and hemoptysis are seen less frequently. In addition, her history of malignancy is a risk factor for thromboemboli.

She could also have pneumonia with pleuritis causing her symptoms. The lack of fever and cough makes this less likely.

Pericardial disease is still a diagnostic possibility. Acute pericarditis can present with pleuritic chest pain. On history, I would ask about common causes of acute pericarditis such as recent viral infections. Pericardial effusion is also possible although the sudden onset of symptoms makes this less likely.

Dr. Koo: Jill, Amit specifically mentioned the absence of hemoptysis. What would the presence of hemoptysis suggest if this patient had a pulmonary embolus?

Jill: Hemoptysis would suggest pulmonary infarction.

Dr. Koo: Michael, you stated that her breast cancer was a risk for pulmonary embolus. Can you expand on risk factors for thromboemboli?

Michael: Virchow proposed a triad of local trauma to the vessel wall, hypercoagulability and stasis as causes of venous thromboembolism. Risk factors would therefore include lower extremity or pelvic trauma or surgery, malignancy, pregnancy, oral contraceptives and other estrogen containing medications and immobilization. In addition, causes of thrombophilia

(tendency to have recurrent venous thromboemboli) include coagulation abnormalities such as protein C or S deficiency, antithrombin III deficiency, activated protein C resistance, antiphospholipid antibodies and plasma hyperhomocystinemia.

Dr. Koo: Can you tell us the rest of her history Amit?

Amit: Her past history includes breast cancer diagnosed in 1998 treated with lumpectomy of the left breast followed by radiation. She is presently receiving chemotherapy.

She is on no medications and has no allergies to any drugs.

Dr. Koo: Amit, can you tell us about the physical exam?

Amit: She appeared anxious. She was in respiratory distress, using her accessory muscles. Her BP was 120/70. There was no pulsus paradoxus. HR was 110 and regular, RR was 24 and her temperature was 37.9° C.

Her JVP was 2 cm above the sternal angle. Her apex was normal. She had normal heart sounds with no murmurs or rubs. Her peripheral pulses were palpable and equal. There was no peripheral edema. Her chest was resonant to percussion. She had normal vesicular breath sounds, symmetrical in intensity with no adventitious sounds. She had a lumpectomy scar. No nodes were palpable. Her abdomen was soft and non tender with no organomegaly, masses or bruits. She had no calf swelling.

Dr. Koo: Nava, has her physical exam helped you with your diagnostic approach?

Nava: Her tachypnea, tachycardia and low grade fever are in keeping with a pulmonary embolus. However, they are not specific and could also be found in pneumonia or pericarditis.

The absence of pulsus paradoxus and elevated neck veins makes pericardial effusion with tamponade less likely.

Her normal chest findings makes pneumonia less likely, but it's still a possibility.

Given the clinical presentation, pulmonary embolus is the diagnosis at the top of my list.

Dr. Koo: Jill, what are the clinical syndromes of pulmonary embolus?

Jill: Patients with massive pulmonary emboli have widespread pulmonary emboli and can present with sys-

temic arterial hypotension and other findings of shock. Those with moderate sized pulmonary emboli can have findings of right ventricular dysfunction. Those with small pulmonary emboli have normal right ventricular function.

Dr. Koo: Amit, what are the physical findings that you would look for in a patient with suspected pulmonary embolus?

Amit: On general inspection, the patient may appear anxious, diaphoretic and cyanotic. They are usually tachypneic and tachycardiac. Their blood pressure would depend on the size of the pulmonary embolus. If massive, the patient can have arterial hypotension. The respiratory exam is usually normal. They may have dullness and decreased breath sounds from a pleural effusion. A pleural rub may be heard. On cardiac exam, I would examine for findings of pulmonary hypertension. Specifically, I would look for an increased JVP, RV heave, loud S2 (specifically the pulmonic component) and pansystolic murmur at the LLSB which increases with inspiration suggestive of tricuspid regurgitation.

I would also examine the patient for findings of a deep venous thrombosis (DVT).

Dr. Koo: Nava, can you tell us what signs you would examine for if you suspected a DVT?

Nava: I would look for swelling of the suspected leg. I would check for a difference in calf swelling of greater than 3 cm when compared to the asymptomatic leg. I would measure this 10 cm below the tibial tuberosity. I would also inspect for nonvaricose collateral superficial veins. In addition, I would palpate for pitting edema and tenderness along the deep venous system of the suspected side.

These findings can be combined with the history in a prediction rule to create risk categories for DVT (Table 1).

Dr. Koo: Jill, what investigations would you order?

Jill: I would order an oxygen saturation, a chest X-ray and a 12 lead EKG. I would also check her CBC, PT, PTT. D-dimers might also be helpful since the patient has no other reason to have formed a clot, such as recent surgery.

Dr. Koo: Michael, what would you expect to see in these investigations if the patient had a pulmonary embolus?

Michael: I would assess for hypoxemia. Some people would also request an arterial blood gas (ABG) but it is important to note that data from the PIOPED (Prospective Investigation of Pulmonary Embolism Diagnosis) study indicate that blood gases lack diagnostic utility for pulmonary embolus and cannot reliably differentiate patients with pulmonary emboli. Hypoxemia or hypocapnia may lead one to suspect pulmonary emboli but are not specific for pulmonary emboli.

The CXR is usually normal but abnormalities in pulmonary emboli include focal oligemia (Westermarck's sign), a peripheral wedge shaped density (Hampton's hump), pleural effusions, elevated hemidiaphragm or an enlarged right descending pulmonary artery (Palla's sign).

The EKG classically shows sinus tachycardia. Other abnormalities seen with pulmonary emboli include T wave inversion in the anterior leads, especially V1-V5. These are probably reciprocal changes reflecting inferoposterior ischemia from compression of the right coronary artery by the right ventricle as a result of pressure overload. You may also see new onset atrial fibrillation or flutter. The complex of an S wave in lead I, a Q wave in III, and an inverted T wave in lead III is specific but rarely seen. Right axis deviation, right ventricular strain or right ventricular hypertrophy may also be seen.

D-dimer is a fragment released as fibrin decomposes. Its levels may therefore be increased in patients with

Table 1 Simplified Clinical Model for Diagnosis of DVT*	
Clinical Parameter	Score
Active cancer (treatment ongoing or within previous 6 months or palliative)	1
Paralysis, paresis, or recent plaster immobilization of the lower extremities	1
Recently bedridden >3days and/or major surgery within 4 weeks	1
Localized tenderness along the distribution of the deep venous system	1
Entire leg swelling	1
Calf swelling by >3 cm when compared with the asymptomatic leg (measured 10 cm below the tibial tuberosity)	1
Pitting edema (greater in the symptomatic leg)	1
Collateral superficial veins (nonvaricose)	1
Alternative diagnosis as likely or greater than that of deep vein thrombosis	-2
*Scoring method: high probability if score is 3; moderate if score is 1 or 2; and low if score is 0. (In patients with symptoms in both legs, the more symptomatic leg was used.)	
Source: JAMA 1998;279, p.1097, Table 7.	

a thromboembolus. However, the D-dimer ELISA (enzyme-linked immunosorbent assay) lacks specificity and levels may be elevated in patients with myocardial infarction, congestive heart failure, pneumonia or cancer and is elevated in those who have undergone surgery.

Dr. Koo: Amit, can you tell us the results of these investigations?

Amit: Her oxygen saturation was 92% on room air. Her CXR was normal. Her 12 lead EKG showed sinus tachycardia at a rate of 110. Her CBC, PT and PTT were normal.

Dr. Koo: Michael, what do you think the diagnosis is and what do you base this on?

Michael: I think that her most likely diagnosis is a pulmonary embolus. Given her clinical presentation and risk factor with no other reasonable alternate diagnosis, the pre-test probability for pulmonary embolus is high.

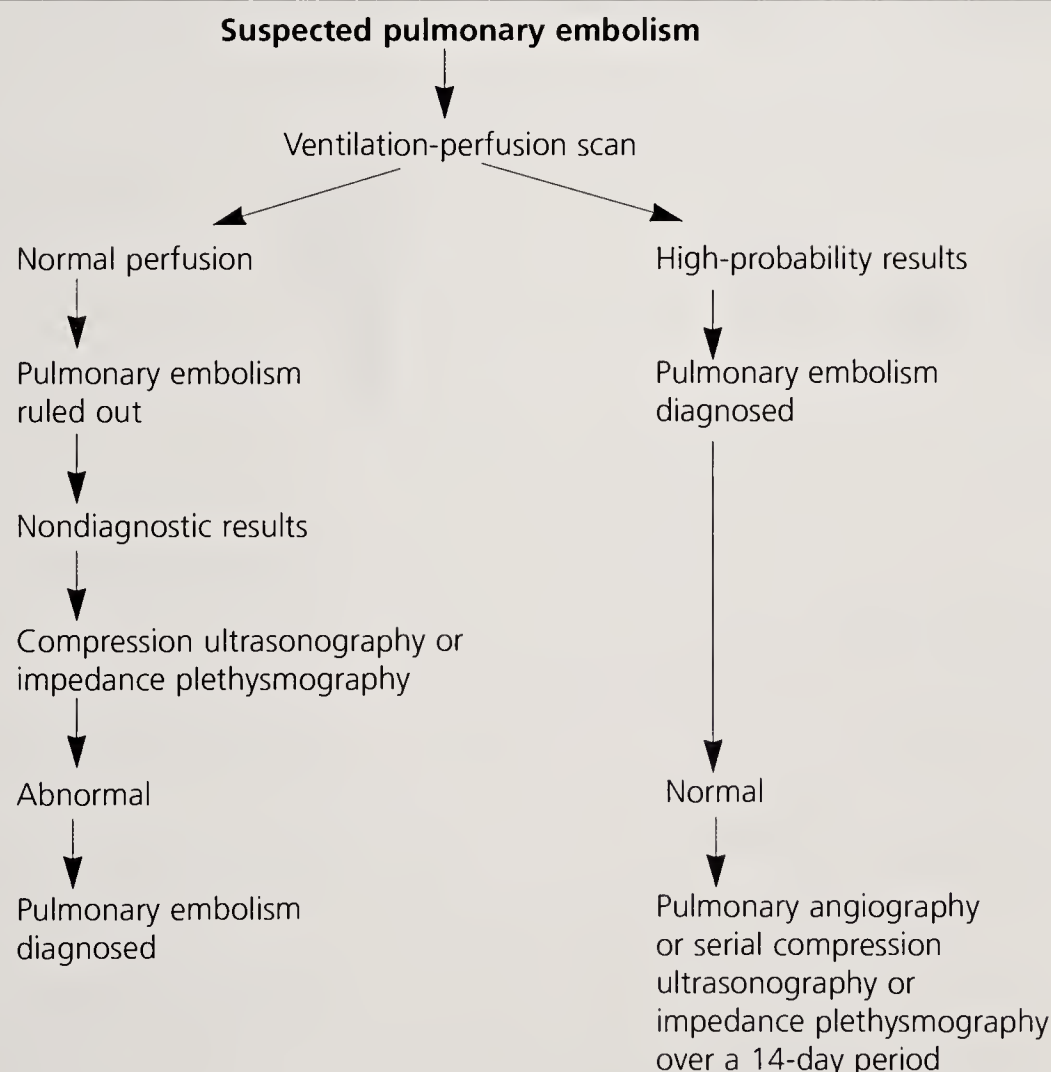
My next investigation therefore would be a ventilation perfusion lung scan. This would be the most useful screening test to rule out clinically important acute

pulmonary embolism. A normal perfusion scan is almost never seen with pulmonary emboli. If there is a high probability result with multiple segmental perfusion defects without corresponding ventilation or chest X-ray abnormalities, the post test probability of pulmonary embolus is very high. With any other non-diagnostic result, given the high clinical suspicion for pulmonary embolus, my post-test probability is still sufficiently high that I would continue with further investigations, such as a compression ultrasound. (Table 2)

Table 2
Percentage Probability of Underlying Pulmonary Embolism According to the Criteria of PIOPED Study

Scan Probability	"Non-Diagnostic"			
Normal/Very Low	Low	Intermediate	High	Clinical Suspicion
Low	2	4	16	56
Intermediate	6	16	28	88
High	0	40	66	96

Source: BMJ 1997;314, pg.426, Table 1.



Nondiagnostic results are those that indicate an intermediate or low probability of pulmonary embolism, or that do not indicate a high probability

Figure 1. An approach to patients with Clinically Suspected Pulmonary Embolism.

Source: NEJM 1996;33, p.1819, Figure 2.

Dr. Koo: That's a reasonable approach. If the ultrasound is normal, what would you do Nava?

Nava: Since the pre-test probability for pulmonary embolus was high, a normal ultrasound would not sufficiently lower my post-test probability to rule out a pulmonary embolus. I would, therefore, do a pulmonary angiogram. (Figure 1). An alternative would be spiral CT scanning, which is a newer technique that is currently being evaluated. This is best for identifying pulmonary emboli in the proximal pulmonary vasculature. However, if normal in the presence of a high index of clinical suspicion, a pulmonary angiogram should be performed.

Dr. Koo: What did you do, Amit?

Amit: A ventilation-perfusion scan was performed which showed multiple segmental perfusion defects that were not matched to ventilation defects. This is consistent with a high probability scan for pulmonary emboli.

Dr. Koo: Michael, how did you manage this patient?

Michael: We anticoagulated this patient. She was started on low molecular weight heparin and Coumadin. The low molecular weight heparin will be discontinued

after approximately 5 days when she is adequately anticoagulated.

Dr. Koo: Thank you very much for presenting this interesting case.

Clinical Pearls

1. The signs and symptoms of pulmonary embolism are nonspecific and can be found in many cardiac, respiratory, and other conditions.
2. Patients have a high pre-test probability of pulmonary embolism if they have risk factors and typical clinical symptoms in the absence of an obvious alternate diagnosis.
3. Arterial blood gases lack diagnostic utility for pulmonary embolism.
4. D-dimers lack diagnostic specificity for pulmonary embolism.
5. Even if the ventilation perfusion scan shows low probability, if the pre-test probability of pulmonary embolism is high, further investigations should be pursued.

Acknowledgements

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Internal Medicine Rounds

Thomas Roger Harris, BSc., and Laura Catherine McAdam, MSc.

Case 1

Dr. R. Myers, M.D., FRCPC

Division of Cardiology, Sunnybrook and Women's College Health Science Centre

A previously well 42 year old woman presented with a three month history of fatigue, progressive shortness of breath on exertion, orthopnea, increasing abdominal girth and peripheral edema. PA and lateral chest X-ray (figure 1) and MRI are provided (figure 2).

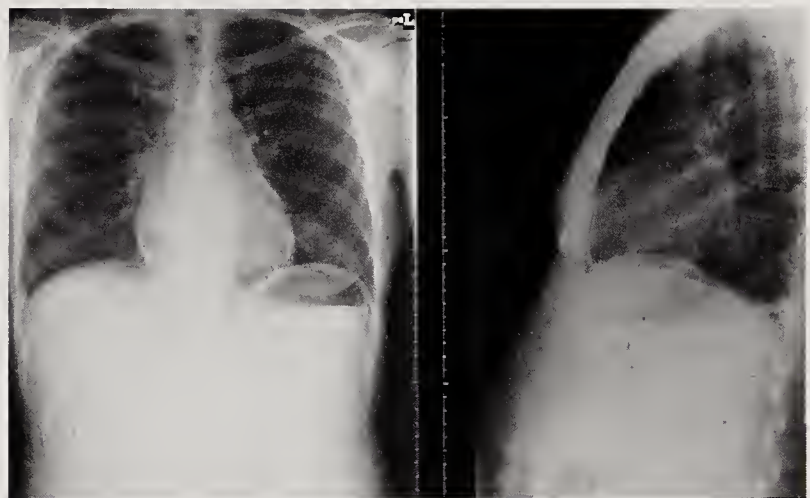


FIGURE 1. PA and lateral chest X-ray

What is the most likely diagnosis?

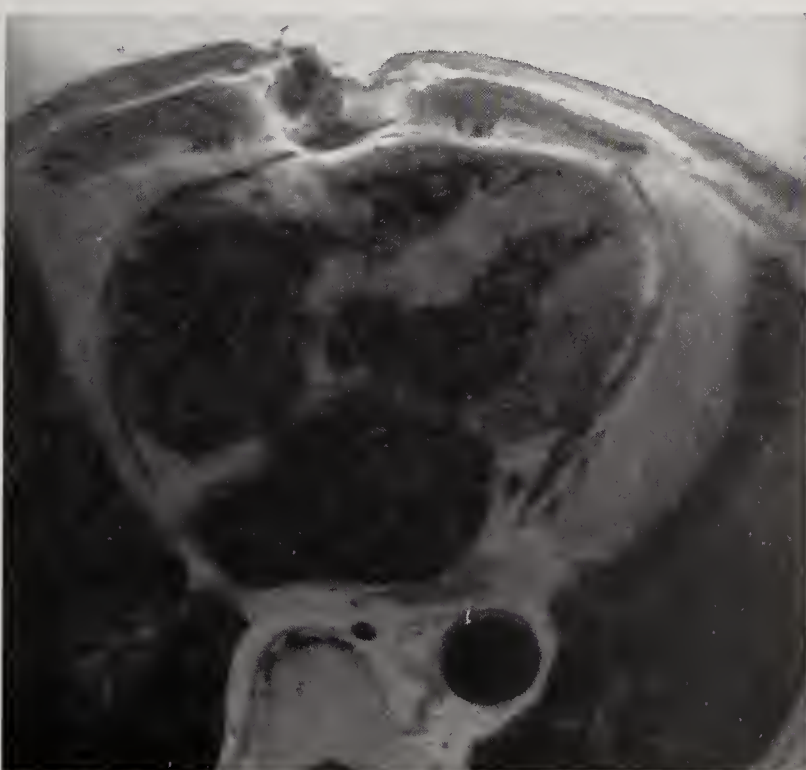


FIGURE 2. T1 weighted magnetic resonance imaging.

Case 2

Dr. C.M. Cheung, M.D., FRCPC

Division of Internal Medicine, Sunnybrook and Women's College Health Science Centre

A previously well 70 year-old female presented to ER with moderate pulmonary edema. She had no previous history of cardiac murmur or heart disease. On examination, she had a loud pansystolic murmur best heard at the apex, in addition to distended jugular veins and bilateral basal rales.



FIGURE 1. Normal trans-esophageal echocardiogram (TEE) showing the normal anterior mitral leaflet (AML) and posterior mitral leaflet (PML) coming together between the left atrium and the left ventricle during systole. LA denotes left atrium and LV indicates left ventricle.



FIGURE 2. TEE of this patient. It shows a flail mitral leaflet (FLAIL MV) that does not join the anterior mitral leaflet during systole.

What is the most likely diagnosis?

Case 3

Dr. C.M. Cheung, M.D., FRCPC

Division of Internal Medicine, Sunnybrook and Women's College Health Science Centre

A 62 year-old male suddenly collapsed. It was preceded by several days of unusual behaviour and confusion. He had been healthy in the past. On examination, he was drowsy and disoriented. There were not any focal neurologic signs. Routine laboratory investigation was normal except for severe hypercalcemia (5.4 mmol/L, reference range 2.2 to 2.6 mmol/L). CT scan of the head showed lesions in the skull but not in the brain.

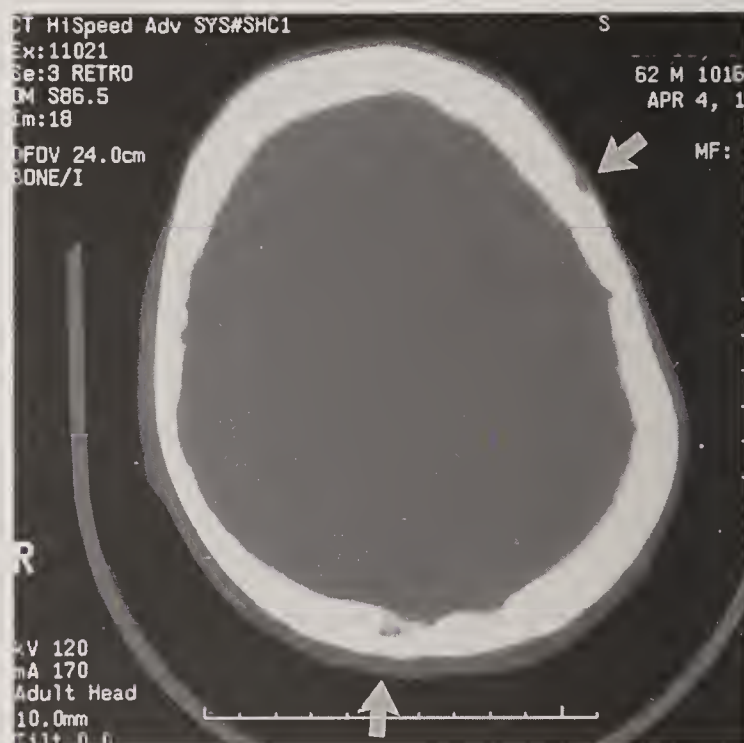


FIGURE 1. CT scan of the head of this patient. The arrows point to the skull lesions.

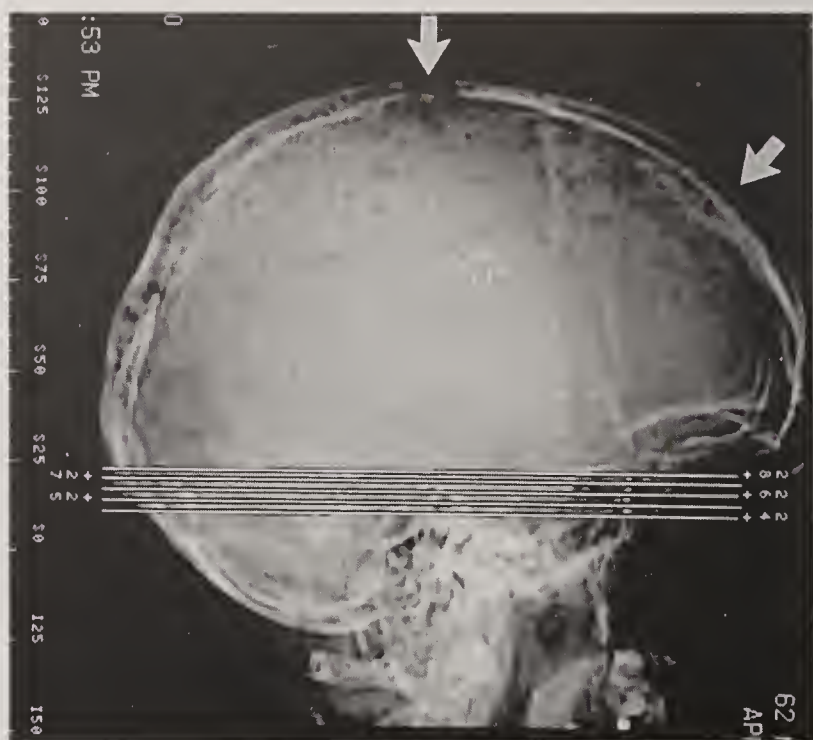


FIGURE 2. Skull X-ray that shows numerous lytic lesions in the skull (arrows).

What is the most likely diagnosis?

Case 4

Dr. M.A. Cooper, M.Sc., M.D., FRCPC

Division of Gastroenterology, Sunnybrook and Women's College Health Science Centre

Mrs. A.F. is a 72-year-old woman who has been in good general health. She presented to her family doctor 4 months ago complaining of fatigue. She was found to be anemic and was started on iron therapy. Her fatigue improved but she began to experience progressive early satiety. She was not on NSAIDs and had no history of peptic ulcer disease. She was seen for an urgent upper endoscopy and at that time was also complaining of a 5 kg weight loss over the preceding 4 months. Physical examination was normal.



FIGURE 1. Endoscopic appearance of the antrum

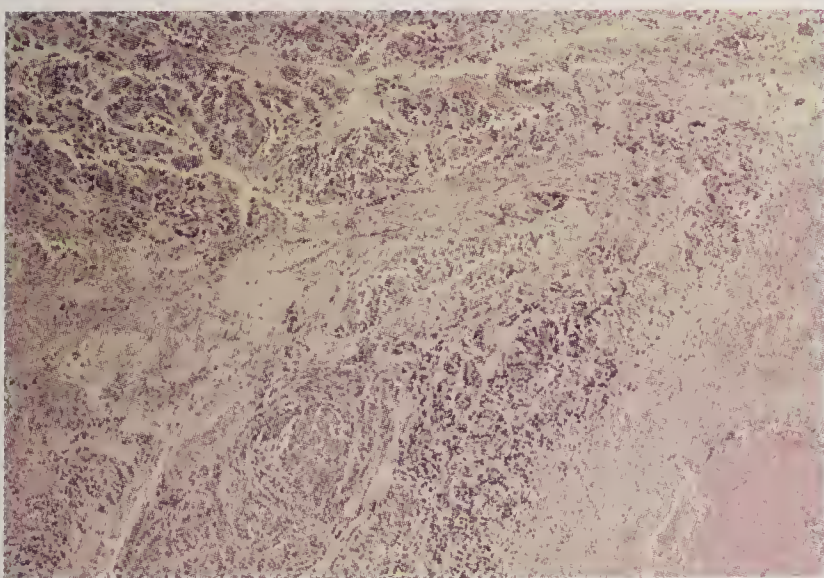


FIGURE 2. Histology of a biopsy from the periphery of the antral lesion
Provided by Dr. L. Geldenhuys M.D., FRCPC (Division of Pathology, Sunnybrook and Women's College Health Science Centre.)

What is the most likely diagnosis?

Case 5

Dr. M.A. Cooper, M.Sc., M.D., FRCPC

Division of Gastroenterology, Sunnybrook and Women's College Health Science Centre

Mr. A.B. is a 64-year-old man with chronic obstructive pulmonary disease (asthma and bullous emphysema). He also has ulcerative colitis for which he has been on Pentasa but recently required prednisone for a flare up of symptoms (currently off steroid). Finally, Mr. A.B. has coronary artery disease that now manifests as stable, exertional angina but he had bypass surgery in 1988 and required PTCA in 1991 and 1992. He was admitted to hospital 2 months previously with an exacerbation of his COPD and unstable angina secondary to a left lobar pneumonia. He was treated with cefuroxime and erythromycin but deteriorated and required intubation. He improved, was extubated, and the antibiotics were discontinued. He suffered a relapse, however, and was found to have pseudomonas pneumonia for which he was treated with ceftazidime and tobramycin and was reintubated. He eventually recovered from this and was convalescing on the ward when he developed diarrhea and hematochezia.

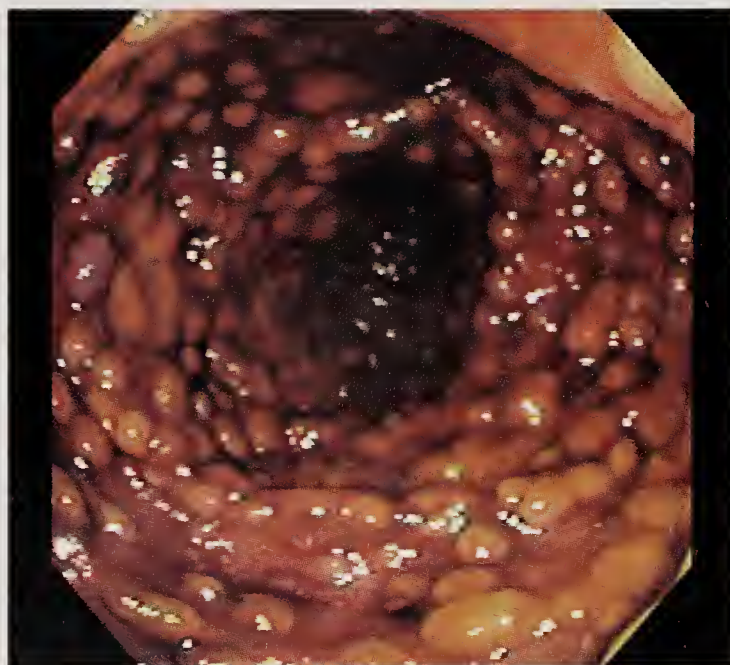


FIGURE 1. Endoscopic appearance of the sigmoid colon.

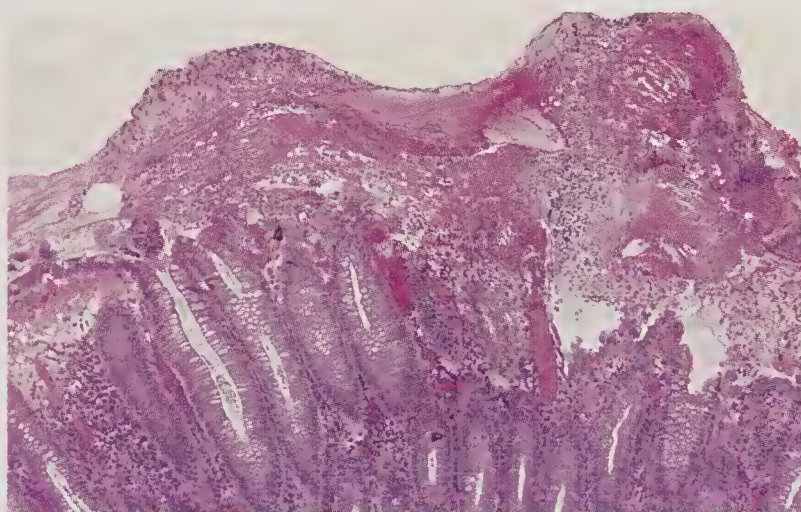


FIGURE 2. Histology of a sigmoid biopsy.
Provided by Dr. L. Geldenhuys, M.D., FRCPC (Division of Pathology, Sunnybrook and Women's College Health Science Centre)

What is the most likely diagnosis?

Case 6

Dr. S. Hutchison, M.D., FRCPC, FACC

Director, Echocardiology and Vascular Ultrasound Laboratories, Division of Cardiology, St. Michael's Hospital

A 58-year-old woman presented with worsening shortness of breath of one week's duration. As well, she had orthopnea and nocturnal dyspnea. For the previous three months she had had tender and stiff joints, and was undergoing a rheumatological evaluation. On exam she had a low grade fever or 38.1°C. The heart rate was 105 bpm, and the respiratory rate was elevated at 22 per minute. There were murmurs of severe aortic insufficiency and mitral insufficiency, and findings of left and of right heart failure.

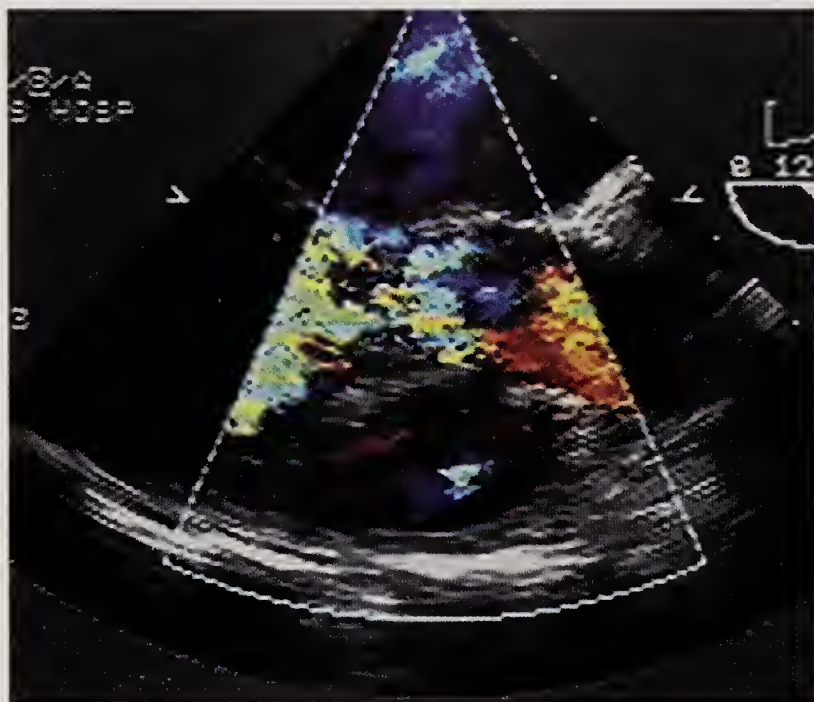


FIGURE 1. Trans-esophageal echocardiogram of aortic valve vegetations.

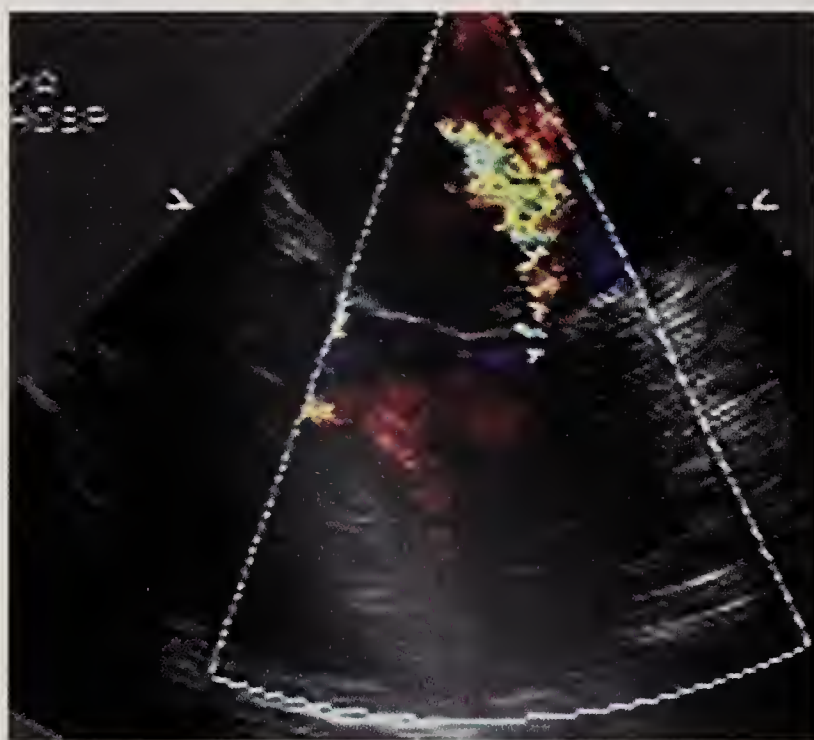


FIGURE 2. Trans-esophageal echocardiogram of mitral valve vegetations.

What is the most likely diagnosis?

Diagnosis

Case 1

Constrictive Pericarditis (CP)

The chest X-ray demonstrates a thin rim of calcification surrounding the cardiac silhouette. The MRI shows pronounced pericardial thickening. The most common etiology of CP, as in this case, remains "idiopathic", presumably the result of a viral infection. CP may also occur after cardiac surgery, as a complication of radiation therapy and is seen in association with tuberculosis, particularly in Third World countries. CP presents with a combination of left and right heart failure symptoms. Examination classically includes an elevated JVP with a prominent Y descent, absence of a pulsus paradoxus, pulsatile hepatomegaly, ascites, peripheral edema, an absent PMI and a pericardial third heart sound or "knock". Diagnostic evaluation includes 2-D echocardiography with specific attention to Doppler flows, cardiac catheterization including right and left sided hemodynamics, CAT scan and MRI. Pericardiectomy is the treatment of choice.

Case 2

Mitral insufficiency due to mitral valve prolapse

Although congestive heart failure is a very common condition, one must try to determine the precipitating cause. The physical examination was strongly suggestive of mitral insufficiency. The diagnosis was clinched by TEE, a somewhat invasive modality that is superior to conventional transthoracic echocardiography in the visualization of the left atrium and the left-sided valves. Mitral insufficiency may be due to rheumatic heart disease, mitral valve prolapse, papillary muscle dysfunction from cardiac ischemia, left ventricular dilatation and infective endocarditis. Her diagnosis was established at the time of cardiac surgery. Her mitral valve was replaced with a prosthesis.

Case 3

Confusion due to hypercalcemia, a complication of multiple myeloma.

Hypercalcemia is most often due to malignancy or hyperparathyroidism. The former usually presents acutely and requires hospitalization. The latter has a very indolent course and is often treated in the ambulatory setting. Amongst the malignancies, myeloma, breast cancer and lung cancer are the more common types associated with this complication. The other (much rarer) causes of hypercalcemia include granulomatous diseases (e.g. sarcoidosis), vitamin D toxicity, milk-alkali syndrome, thiazide diuretics and hyperthyroidism. This patient was diagnosed to have myeloma with the presence of monoclonal peak on serum

protein electrophoresis and an abundance of plasma cells in the bone marrow. The skull lesions are myeloma deposits in the skeleton. The hypercalcemia was successfully treated with fluid, furosemide, calcitonin and bisphosphonate.

Case 4

Malignant Gastric Ulcer

This woman's clinical course suggested an ominous condition that was confirmed by endoscopy and biopsy. The ulcer was large and deep, with heaped up folds around the periphery. The tissue was hard when biopsied. The histology confirmed an infiltrating adenocarcinoma of the stomach.

Case 5

Pseudomembranous Colitis

Clostridium difficile is a gram positive organism that confers disease in humans by the production of toxins. In humans it is toxin A that is most pathogenic. It causes loosening of the tight junctions in the epithelium and induces inflammation resulting in a cellular, protein-rich exudate. Mild

cases present as a watery diarrhea and the colonic mucosa will appear erythematous and friable. More serious cases result in pseudomembranous colitis with watery diarrhea, cramps, tenesmus, and perhaps an ileus and megacolon with a risk for perforation. Approximately 10% of patients will have a bloody diarrhea. The gross and microscopic appearances are as shown. It rarely can occur spontaneously but usually results after the administration of antibiotics which cause an alteration in the normal bowel flora. Treatment consists of stopping the offending agents if possible and using metronidazole and/or vancomycin.

Case 6

Infective Endocarditis

The patient had infective endocarditis with *Streptococcus viridans*, resulting in destruction of the mitral and aortic valves, and severe, acute, congestive heart failure of the basis of valve insufficiency. The trans-esophageal echocardiographic images demonstrate the hallmark findings of large vegetations on the valves and valvular insufficiency. There was as well a polyarticular arthritis, which was believed to be endocarditis associated.

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Three-Dimensional Conformal Radiotherapy - Method of Choice for the Treatment of Localized Tumours

Karol Wroblewski (OT2)

Neoplasms are treated most effectively using local-regional treatment such as surgery and radiation therapy, when it is still in the form of a localized tumor with no distant metastases. While surgical procedures often result in organ destruction, radiation therapy offers the benefit of organ preservation. However, standard radiotherapy (SRT) methods do not allow for a precise localization of tumors and large safety margins have to be used. As a result, a significant amount of normal tissue in the vicinity of the tumor receives a full dose of radiation. Restrictions on the radiation dose (to the tolerance level of the normal tissues) consequently limit the effectiveness of SRT.



FIGURE 1. The prostate and the seminal vesicles are shaded in orange. Green colour indicates the region which absorbs the full dose of radiation when SRT is used to treat the prostate, and which is not exposed to full radiation dose when 3DCRT is used. 3DCRT allows for protection of significant portions of the bladder and rectum.

Three-dimensional conformal radiotherapy (3D CRT) is a new method developed to overcome the above problem by allowing for a precise localization of the tumor. The key of the 3D CRT is the computer-assisted assembly of two-dimensional images into a 3D model for a three-dimensional radiation treatment planning system. After determining in which region of the body the tumor is present, a set of CT scan images is obtained (other 2D images such as MR or PET scans can also be acquired if necessary). Computer

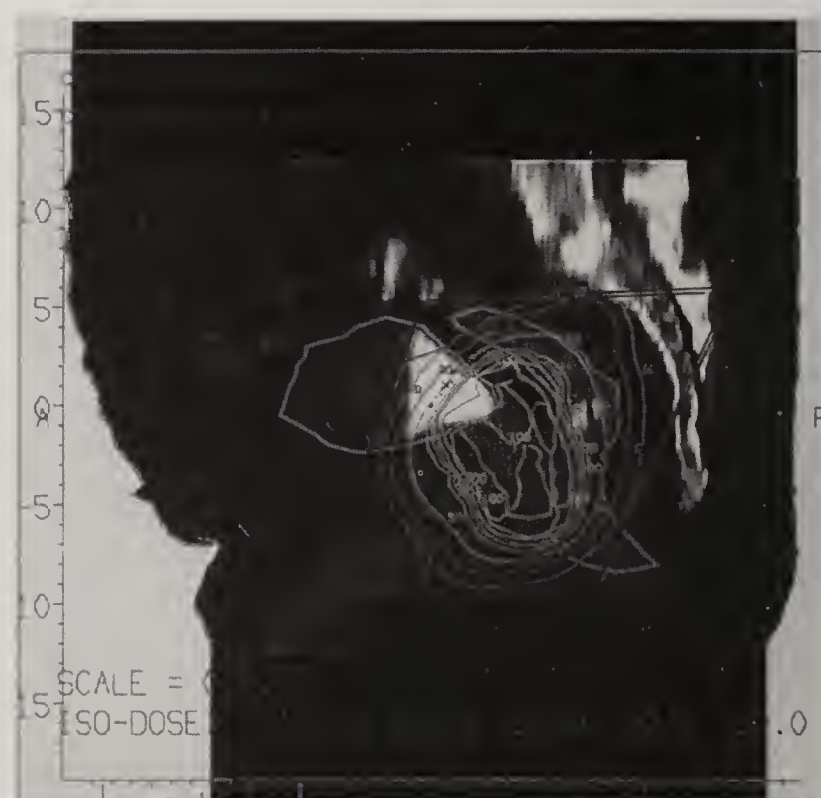


FIGURE 2. Transverse and side view CT scans showing radiation isodoses superimposed. The concentric lines circling the prostate on both views indicate the shaping of the radiation area with the maximal sparing of the neighbouring rectum and bladder. The top view also shows the entrance angles of the six radiation beams.

software digitizes and combines the information from the 2D images into a 3D model of the tumor and the surrounding area, which can be rotated and viewed from different angles. Once optimal angles are specified, it is possible to look at the tumor with "beam's eye view". This allows one to observe the contour of the tumor from this particular direction. Multileaf collimator, a device in the head of the linear accelerator, then adjusts the shape of the beam to the contour of the tumor. It has a large number of small leaves each of which can be moved and positioned individually, to give the beam the desired shape.

3D CRT offers several advantages over standard radiotherapy treatment. Beam shaping allows for the use of smaller safety margins, which results in a smaller amount of normal tissue being irradiated, and consequently produces less severe side effects. Because of a greater number of beams used to deliver the total radiation dose in 3D CRT, the tissues through which these beams have to pass absorb less radiation. Directing the radiation onto the tumor from directions other than anterior, posterior and lateral (as it is done in SRT) can make it possible to avoid irradiation of structures which have low radiation tolerance. Finally, 3D CRT makes it possible to deliver a higher radiation dose which makes the treatment more effective.

3D CRT is used to treat many kinds of tumors, but it is used most extensively in the treatment of prostate cancer. Dr. Juanita Crook from Princess Margaret Hospital in Toronto is an associate professor of radiation oncology who specializes in the treatment of prostate cancer using this technique. She explains why the tumors of prostate are such good targets for 3D CRT: "First of all prostate is really well imaged with CT. Then, the prostate is in very close proximity of the rectum and bladder, organs that have low radiation tolerance. Thus sparing these organs by conforming the shape of the radiation beam and minimizing the margins is very important. Finally, in SRT the radiation dose is limited to 65-66 Gray. With 3D CRT the dose can be escalated to about 71 Gy. Since in the region between 60 and 80 Gy the response increases very rapidly with increasing the dose, increasing the dose by 5 Gy makes the treatment much more effective."

Several published clinical studies show that the use of 3D CRT for the treatment of prostate cancer is more effective than the use of SRT. In the study conducted at Fox Chase Research Center 373 prostate cancer patients were treated with 3D CRT and 129 with SRT. The follow up observations demonstrated 3D CRT to be superior in 12 month prostate specific antigen response, clinical absence of disease, and acute morbidity. 79% of the patients treated with 3D CRT had no tumor recurrence in 24 months as com-

pared to only 48% who did not have recurrence when treated with SRT with doses smaller than 71 Gy.

3D CRT is certain to become more common and widely used in the future. It offers a double benefit of lowering the treatment's toxicity while improving prognosis.

Acknowledgements

The author would like to specially acknowledge the help of Dr. Juanita Crook in the preparation of this article.

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The GeneChip® Revolution: The Next Generation of Genomics

Filio Bilia, Ph.D (OT1)

The first explorations into global gene expression were undertaken in the mid-1970's.¹ These initial studies provided the basis for our current understanding of the various mRNA subclasses; high, intermediate and low abundances genes. In the 1990's, a new era for gene expression has unfolded as a result of extraordinary technological advances. While there are several approaches for studying global gene expression including large-scale sequencing of the human genome and global amplification of cDNA from samples as small as single cells,² the GeneChip® makes possible the simultaneous examination of the expression of thousands of genes in a single experiment.

To generate an expression GeneChip®, cDNA clones are robotically printed on a glass slide in a microarray about the size of a microprocessor and subsequently hybridized with two different fluorescently labeled probes. The probes are cDNA populations generated from cells or tissues in two physiological states of interest. Using a laser confocal fluorescent microscope, fluorescent intensities are produced and intensity information is obtained following image processing. As many as 100,000 entities can potentially be printed on the GeneChip®.

The importance of this technology is reflected in the initiation of 'The Microarray Project', a collaborative research effort between the numerous divisions of the NIH including the National Human Genome Research Institute, National Center for Biotechnology

Information, National Cancer Institute and many others. The goal of this project is "...to develop arrays which contain every gene in the genome against which mRNA expression levels can be quantitatively assessed."³ On the commercial front, a Californian firm, Affymetrics, Inc. has made it possible for researchers, commercial and academic, to order GeneChip®-related services in the United States, Canada, Western Europe and Japan. In addition, Affymetrix has entered into agreements with companies such as Eli Lilly and Company, Molecular Applications Group, Hewlett Packard, Beckman Coulter, Human Gene Sciences, Inc., Roche Molecular Systems and many others, to develop new bioinformatics software, to provide access to the microarrays for research and development, drug discovery research and therapeutic development, to develop a bacterial microarray and to generate a new generation of diagnostic kits for applications in HIV drug resistance and p53 for cancer staging.⁴

The capability of such technology is unprecedented. The cDNA microarrays currently available from Affymetrix contain about 30,000 murine genes and expressed sequence tags (ESTs) and 40,000 human genes and ESTs. While the costs of a complete GeneChip® assay is high, the rewards far surpass the time required to do an equivalent number of Southern hybridizations, a task that would literally take years. The major limitations to the expression GeneChip® technology, however, lies in its inability to represent the entire human genome,⁵ believed to contain about 70 000 genes as well as at the level of the analysis limited by the software available.⁶

DNA microarrays printed with oligonucleotides have also been generated to examine mutations and polymorphisms in genes such as p53, BRCA-1, BRCA-2, cytochrome p450 and HIV.⁷⁻⁹ These microarrays allow for the systematic and comprehensive scanning of an entire gene. More recently, Affymetrix is involved in the production of disease-specific chips that could detect all known genetic aberrations for a particular condition. One of the first of this type is the 'cancer gene' chip. As more and more is understood about the human genome, there will be an increased potential for similar chips to be generated for conditions such as heart disease, hypertension, diabetes, and conditions such as schizophrenia. None of these diseases are caused by a single gene mutation, and the GeneChip® technology could offer the precise examination of an individual's genome and predisposition. It has been suggested that the microarray technology will do for genetic medicine what the microprocessor has done for Intel.

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Conn's Current Therapy 1999

Reviewed by Lilia Malkin, BSc. (OT1)

Editor: Robert E. Rakel

Publisher: W.B. Saunders Company

Date of Publication: 1998

Number of Pages: 1340

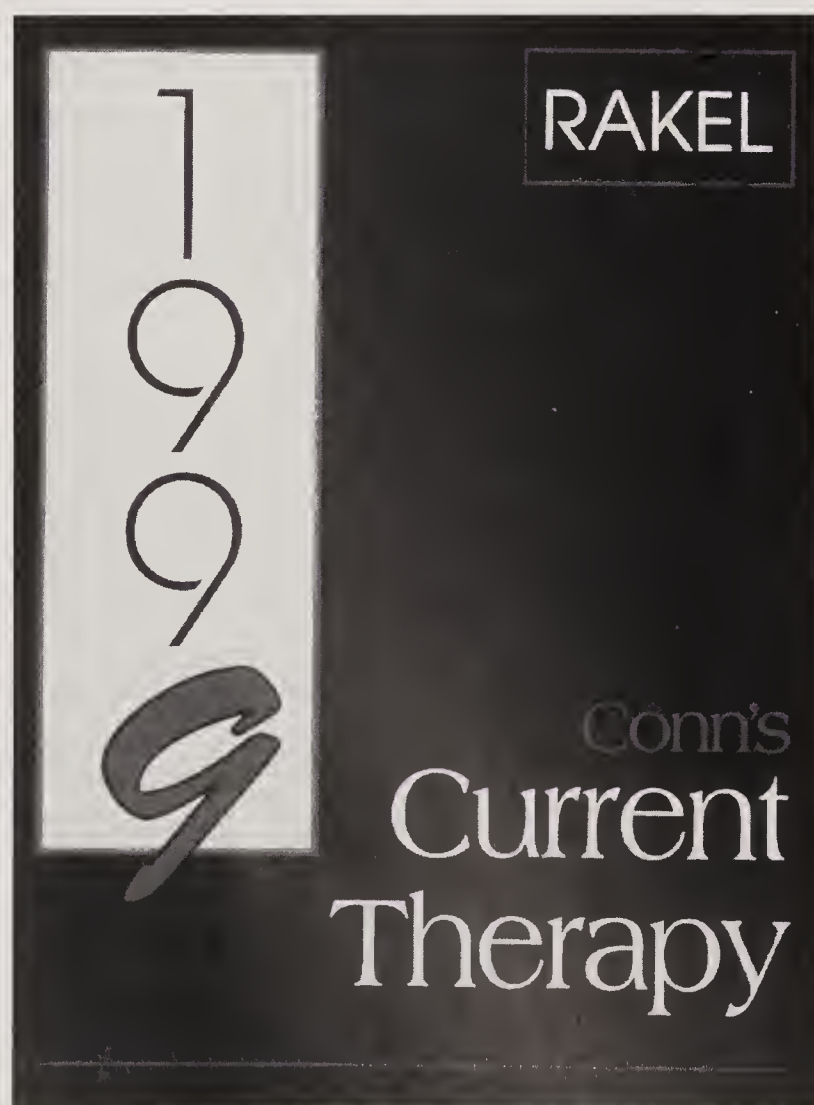
Price: \$85.55

Overall: 8/10

Strengths: Chapters logically organized according to body systems affected by disease; additional chapters on symptomatic care, infectious diseases, and injuries. Listing of new medications.

Weaknesses: Potential for biased treatment recommendations. No additional references offered. Few illustrations.

Audience: Medical students; Family Medicine residents and practising physicians.



Conn's Current Therapy 1999 is the fifty-first edition of an annual publication that is designed to aid the practising physician keep abreast the current trends in treatment of diseases that commonly present in the family practice setting. Every year, international experts from a wide variety of medical fields are asked to contribute the latest approved methods of treatment for specific symptoms and diseases. The authors differ from year to year in attempts to keep the material in each edition as "fresh" as possible. In his preface to the publication, the editor encourages readers to compare the treatment methods presented in the new edition to the approaches offered in previous years in order to gain additional perspectives on management of a given clinical problem. Each yearly edition also features new topics, broadening the scope covered by the book. Since the audience for this reference text is made up predominantly of North American health care practitioners, the authors strive to cover primarily those topics that are of interest and importance to the US or Canadian physicians.

A superior feature of this text is its organization into eighteen sections in a manner that makes specific topics easily accessible to the reader. The first section, entitled "Symptomatic Care Pending Diagnosis" may be one of the most useful in the book. It covers a wide variety of topics, which range from

pain to hiccups. Other highly practical sections are "Infectious Diseases" and "The Sexually Transmitted Diseases". A fascinating "Physical and Chemical Injuries" section includes articles on treatment of common clinical problems, such as burns and poisonings, as well as less common injuries, such as those acquired by exposure to hazardous marine animals. The remaining sections are devoted to groups of symptoms or diseases classified under specific physiological systems. Treatment of respiratory, cardiovascular, circulatory, digestive, metabolic, endocrine, genitourinary, allergic, dermatologic, obstetrical/gynecological, psychiatric, and nervous system disorders is discussed in a concise and highly readable fashion. Other useful features include an appendix describing the reference values for interpretation of laboratory tests in both conventional and SI units, a listing of new pharmacologic agents available in 1997, and a comprehensive index that allows easy access to specific treatments in the text.

This text is highly valuable, since it combines the most recent treatment strategies for a broad range of clinical problems in one publication, allowing the busy physician (or physician-in-training) to follow the current clinical practice standards, while minimizing the time involved in searching for that information. Indeed, it is much like having a stack of highly relevant review articles at one's fingertips!

There are, however, several drawbacks in this otherwise highly effective text. Since *Current Therapy* is primarily a reference, rather than a textbook, the background information provided at the introduction of each chapter may not be sufficient for those with limited knowledge of a given disorder. The chapters are not accompanied by references, an inconvenience in cases where one would like to refer to the primary research articles for additional, more in-depth information. While many sections are quite extensive in the coverage of a

broad range of topics, others are disappointingly less so. For instance, the "Psychiatric Disorders" section is quite brief at only thirty pages, the coverage being quite disproportionate to the amount of psychiatric illness seen and treated by family physicians. Lastly, and perhaps least significantly, illustrations are sparse, detracting from the aesthetic appeal of this otherwise well-presented publication.

In summary, despite minor shortcomings, this text is well organized and quite readable. *Conn's Current Therapy 1999* is an excellent reference for current treatment information on the large variety of clinical problems encountered by medical students, residents, and practising physicians in primary care medicine.

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The Yearbook of Cardiology, 1998

Reviewed by Stephen Wilton (OT1)

Editor in Chief: Robert C. Schlant, M.D.

Publisher: Mosby

Date of Publication: 1998

Number of Pages: 552

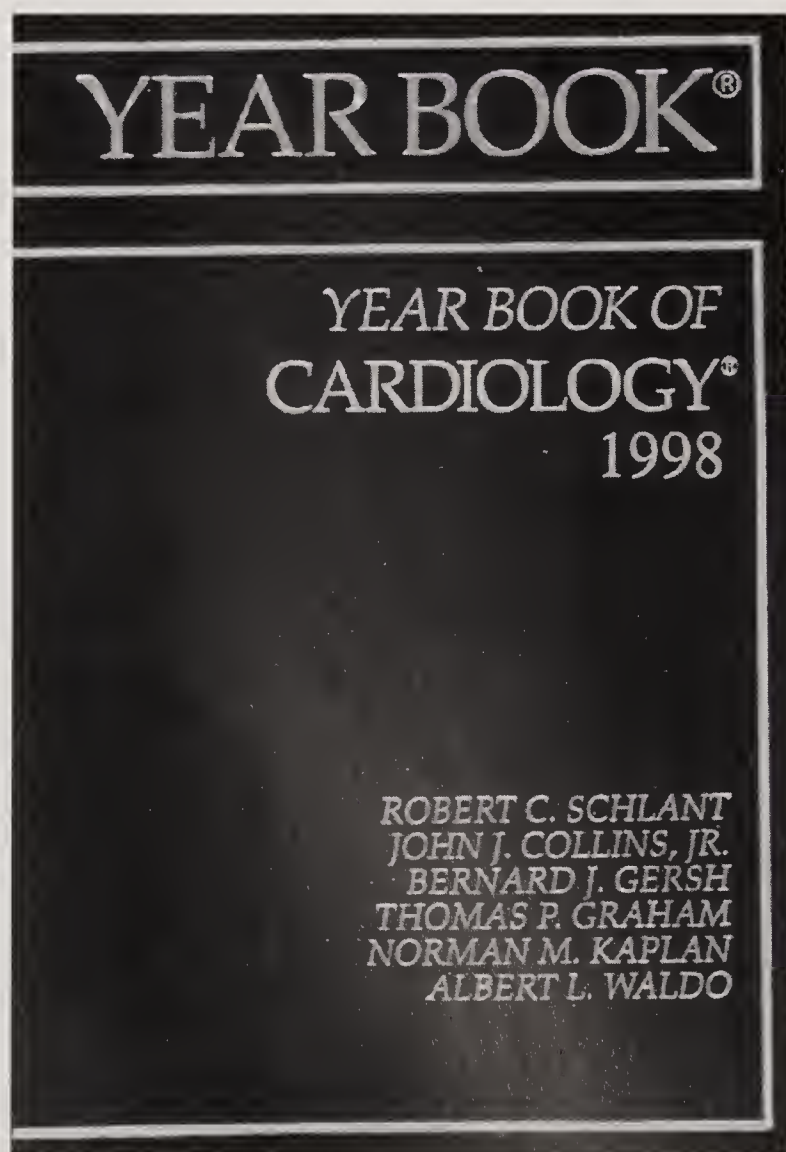
Price: \$120 per year

Overall: 8/10

Strengths: Concise review of developments in cardiology, standardized abstract format, well-indexed.

Weaknesses: Editorial comments are often unenlightening, too few references.

Audience: Practicing physicians and postgraduate trainees.



The Yearbook of Cardiology, 1998 is one of a series of literature surveys published by Mosby, that attempts to distill the year's relevant literature into a compact one-volume format suitable for review by the busy physician who wants to keep abreast of developments in his or her area of practice. The series covers 40 specialties with individual editions, surveys over 1,000 journals published worldwide, and last year reviewed over 250,000 original articles. This volume alone contains abstracts of over 400 articles from 60 recognized journals. It is divided into six sections covering the major areas of cardiology research. Each page-long abstract follows a standard format, presenting Objectives or Background, Methods, Results and Conclusions, accompanied by a few lines of commentary from the section editor. For some entries one or two references for further reading are provided.

The best thing about this book is that it accomplishes exactly what it set out to, no more and no less. It provides a thorough yet concise review of a year's worth of research in cardiology from around the world, in a format both accessible and affordable to the practicing cardiologist or cardiologist-wannabe. One aspect in the life of a medical professional that is always at a premium is time, a fact that makes it virtually impossible to keep up with current literature. Subscribers to this service however, can easily review the year's developments in basic science and clinical

research in an area of interest, e.g. coronary heart disease, in a single night of reading. The cost of the volume, being roughly equal to that of a one year subscription to a scientific journal, seems very reasonable considering the breadth and depth of the publication's coverage.

The potential value of this service would not be realized, however, if the writing of the abstracts was not so effective. One key feature of this publication is that all of the abstracts are written by Mosby staff, rather than merely reprinting the authors' original abstract. This provides two important advantages. First, it frees them from having to rely on the authors' ability to effectively summarize their work. Second, and more importantly, it allows for a standard format throughout the book, which gives the reader an idea of what to expect from each article, and a way of judging its significance relative to other work. The common format works very well, and overcomes some of the grievances typically encountered with scientific writing. The background and methodology are understandably brief, but to the point. The results section is refreshing, as only the most important findings are presented, with little reliance on statistical jargon to confuse the point. Another nice feature is that abstracts with similar themes are grouped together, creating a seemingly seamless flow from one topic to the next. These aspects combine to make the book an easy read, even for those unfamiliar with cardiology. This reviewer, a borderline narcoleptic who is not in the habit of reading scientific literature for pleasure, was able to maintain interest and consciousness while reading through one section until quite late at night: a resounding endorsement.

In addition to its great format and effective writing, the Yearbook is also aesthetically pleasing. The volume is handsomely bound, and the figures and black & white photographs which are interspersed throughout the text are helpful, and of fine quality. Also, quickly finding articles on a favorite topic or by a specific investigator is no problem, as it is thoroughly indexed by both subject and author.

There are a couple of problems with the book, both of which are relatively minor. The first is that the comments written at the end of each abstract by one of the editors do not serve their intended purpose. Most of these comments are of the, "Gee, old so-and-so sure did a heck of a job on this one", variety, and offer little in the way of new information or constructive criticism. Perhaps this space could be better used to expand the list of references given for each article, which is currently limited to one or two, if any.

In summary, *The Yearbook of Cardiology, 1998*, and presumably its companion volumes, provide an excellent way for the practicing physician or postgraduate trainee to keep up with developments in her or his field, without going to great expense in either time or money. While certainly not required reading for the undergraduate medical student, the *Yearbook* series is something to keep in mind for future use, and would make a valuable addition to hospital library collections.



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Robbins Pathologic Basis of Disease, 6th edition

Reviewed by Amy Tam (OT2)

Authors: Ramzi S. Cotran, Vinay Kumar and Tucker Collins

Publisher: W.B. Saunders Company

Date of Publication: 1999

Number of Pages: 1425

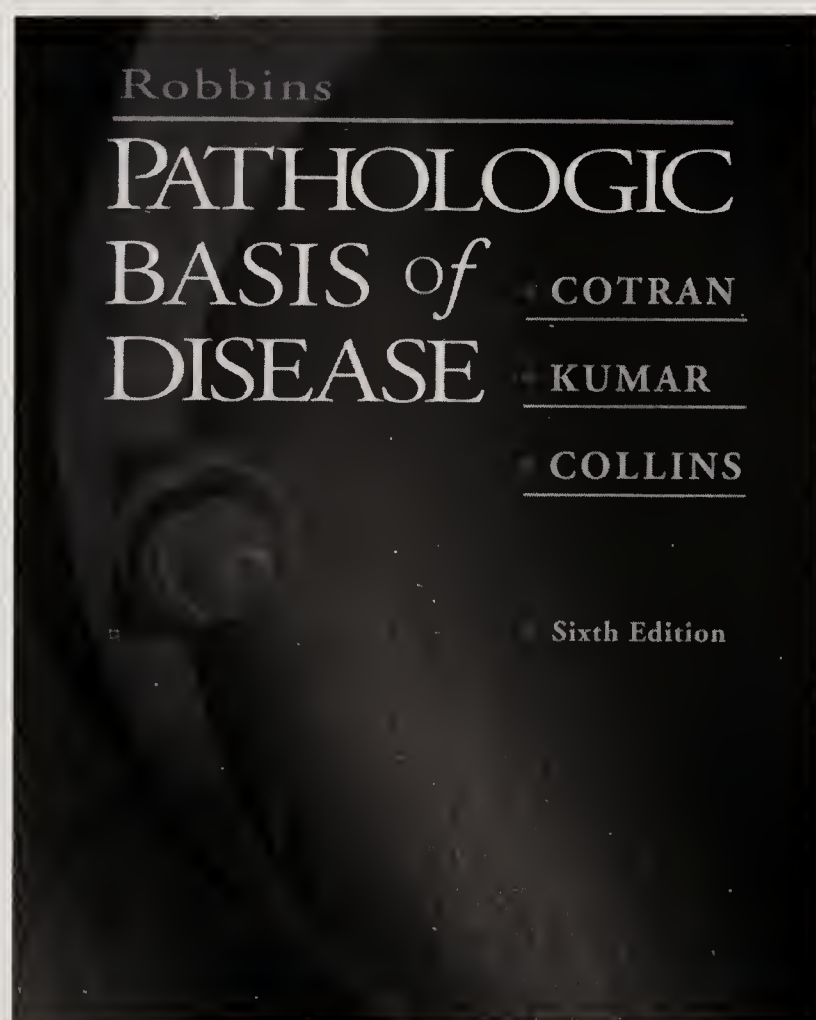
Price: \$117 Canadian

Overall: 8.5/10

Strengths: Up-to-date, clearly written.

Weaknesses: First section has minor organizational problems and a few figures that do not always add to the text; large proportion of the electron micrographs are blurry.

Audience: Undergraduate medical students.



This year, Cotran, Kumar and Collins bring us the 6th edition of *Robbins Pathologic Basis of Disease*, a companion text for introductory pathology courses. Updated once every five years, this new edition has undergone many text and figure revisions. All of the black and white figures have been replaced by colour figures, greatly enhancing the text's overall appearance and quality. Like its predecessor, the book is divided into two parts: the first third deals with general pathologic mechanisms, while the remaining two thirds focuses on disorders that affect individual organ systems.

The introductory chapters encompass cellular injury and repair, and the mechanisms behind hemodynamic, genetic and immune disorders, neoplasia, infectious diseases, and diseases associated with the environment and nutrition, as well as infancy and childhood. This layout creates organizational challenges, and this is one facet in which the text is lacking. The subject material is developed in a progressive manner, but discussions about molecular biology, biochemistry and immunology that are fundamental to many of these initial chapters are presented in isolated fragments. In several instances, cru-

eial concepts are discussed assuming the reader has prior knowledge while the concepts are presented in later sections at an introductory level. Although those who are well versed in these topics will not find this problematic, a reader who is a relative newcomer to these areas will be frustrated. Due to this organizational weakness, I was left with the impression that some of the chapters were geared toward different audiences. Generally, though, the text is well written and very clear. It includes many fascinating discussions, notably those chapters on immune diseases (which includes a large section on acquired immune deficiency syndrome), neoplasia, infectious diseases and environmental and nutritional pathology.

Organization aside, I have only a few minor criticisms, and they all concern the first portion of the text. The opening chapter has a number of schematics that are too simple to contribute to the reader's understanding. There are also instances in the first third of the text where more figures accompanying the morphology discussions would have been helpful. Moreover, a significant proportion of the electron micrographs reproductions have decreased in quality relative to the last edition.

The authors find their niche in the remainder of the text,

which is devoted to individual organ systems. The material is well complemented with figures, schematics and tables. Although occasionally I found the discussions on individual diseases to be too general, a high degree of detail cannot be expected in an introductory level text with such a large breadth. The writing is also consistently of high quality in this section. Each chapter begins with background information on normal structures, then discusses pathology, complete with morphologic changes. With more clinically significant conditions, the epidemiology and expected course of the disease are included with the discussion.

Overall, *Robbins Pathologic Basis of Disease* makes a fine introductory text and will serve as a handy reference throughout medical school and residency. The price may seem steep, but the book covers a vast amount of subject material, and does it well. Undergraduates and residents will appreciate the authors' careful presentation of current research, which illuminates the text and inspires readers. The weaknesses highlighted here are far outweighed by the clarity of writing, the overall quality of the figures and the excellent reference lists. The text reaches a level that will give students confidence in their knowledge, and that makes this book one worth owning.



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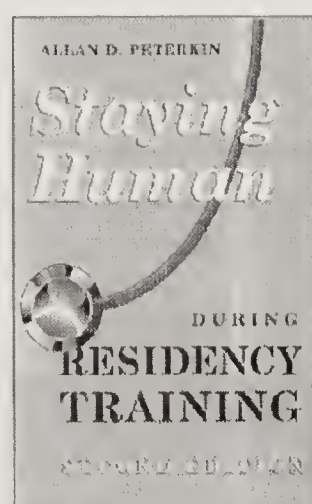
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Procedure for Submission

Contributions should be addressed to: The Editors, *UTMJ*, Medical Sciences Building, Room 2141, 1 King's College Circle, University of Toronto, Toronto, Ontario, M5S 1A8, Canada; Phone: (416) 946-3047. The paper should be submitted by an author, preferably the principal author, who should indicate in a covering letter:

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2. the exact address to which all related correspondence should be sent and the telephone and FAX numbers at which the author can be reached;
3. that neither the submitted manuscript nor any similar paper, other than an abstract of preliminary communication, has been or will be submitted to, or published, in any other primary scientific journal;
4. that all of the authors are aware of, and agree to, the content of the manuscript and that authorization has been given to use any information conveyed by either personal communication or release of unpublished experimental data;
5. three to six key words describing the paper, to assist in the selection of the reviewers.

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1. The author's covering letter containing the above information.
2. **Four** copies of the manuscript and **four** sets of original illustrations. Illustrations should be Camera-Ready black and white photographs, figures, line drawings, and graphs.
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Article in a book or comparable publication

2. Norris KE, Norris F, and Brunfeldt K. (1980). *Nucleic Acids Synthesis: Applications to Molecular Biology and Genetic Engineering*. Koster H (ed). IRL Press: London, pp. 233-241.

Books, theses, or comparable publications

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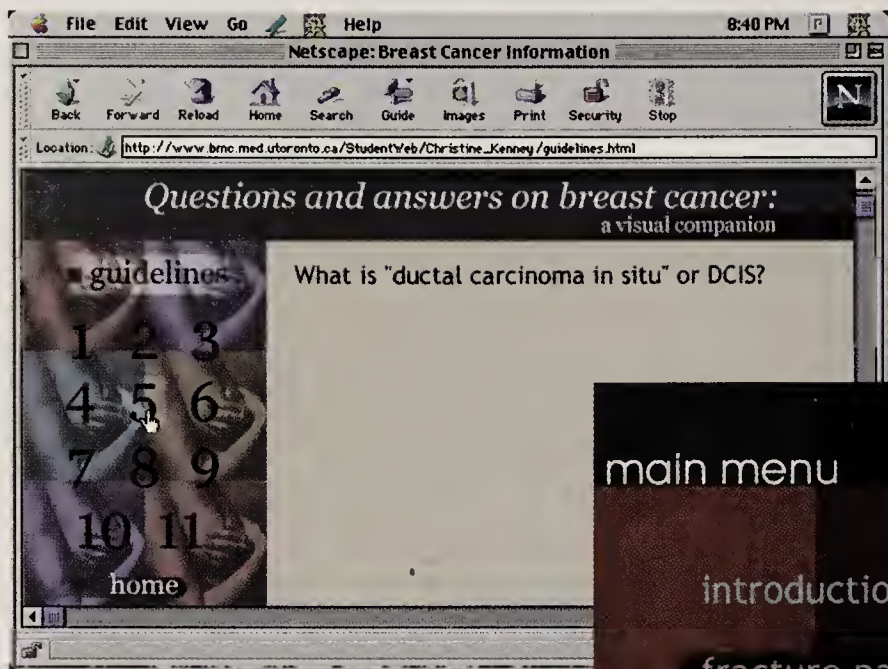
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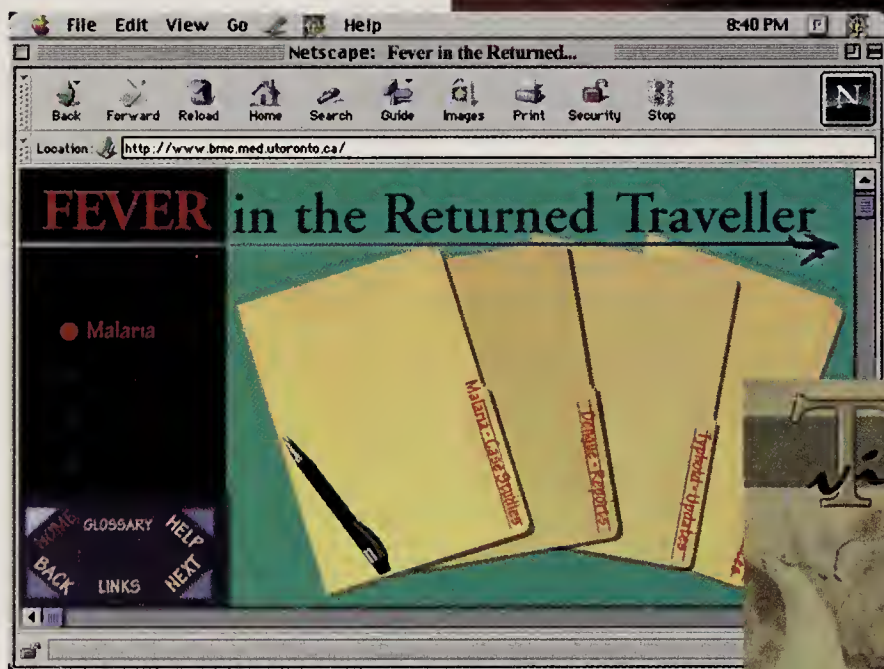
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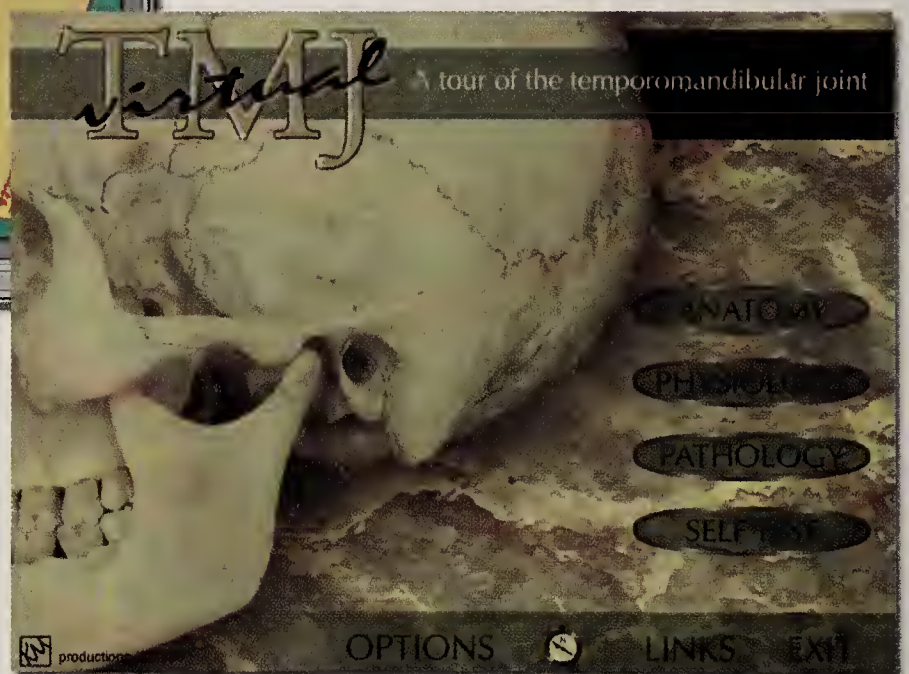
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